EXHIBIT 130

RISK MANAGEMENT PLAN
for
OPIOID ANALGESICS
FOCUS ON: OXYCODONE ER

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ENDO Pharmaceuticals, Inc.
100 Painters Drive
Chadds Ford, PA 19317
Telephone: (610) 558-9800
Toll Free: (800) 892-6131
Facsimile: (484) 840-4295

CONFIDENTIALITY STATEMENT

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1. BACKGROUND

As a pharmaceutical company focused on the improvement of pain management, Endo Pharmaceuticals Inc. (Endo) feels a strong sense of responsibility to improve the care of pain patients while at the same time safeguarding against potential misuse of its products. Improving pain management includes the development of novel effective analgesics, making available generic pain medicine, and also ensuring the proper and appropriate use of its medication. Thus, Endo Pharmaceuticals Inc has developed and is constantly striving to improve a comprehensive "Risk Management Plan (RMP) for Opioid Analgesics," which aims to promote the safe and responsible use of the product while concurrently minimizing opioid abuse, misuse, and diversion through appropriate drug labeling, tight controls on distribution, proactive pharmacovigilance, extensive education, and funding of clinically meaningful research. These efforts are designed to address the three key elements of a Risk Management Plan as identified by the FDA 1) minimize risk of accidental exposure 2) minimize risk of abuse and misuse and 3) minimize risk of improper patient selection. Outlined in this document are the segments of Endo's "RMP for Opioid Analgesics" that will pertain to Oxycodone ER generic.

While the FDA has not ruled that an approved RMP is required for generic drug products, Endo understands the need for a voluntary program that will minimize opioid abuse, misuse, and diversion, particularly in the light of the circumstances surrounding the RLD (Oxycontin®). There are certain features about Endo's RMP which take into account the somewhat different problems that were encountered with the Oxycontin® product, which may not be operational when Endo's product is approved. It is critical to understand that Endo's Oxycodone ER is an AB rated generic drug and, therefore, the customers for generics are retailers and wholesalers and not physicians. Specifically, it is important to recognize that it is the efficiency and automation of the trade including retail pharmacy chains, wholesale distributors, and institutional buyers, which drives sales of the generic and conversion of the brand. In addition, the policies and pressures from HMOs, Medicaid, insurance companies, and the general public drive lower cost substitutions for expensive branded products. Thus, Oxycodone ER's generic sales and

marketing activity will be limited to contracting with and supporting these trade and institutional companies and organizations.

Thus, Endo's RMP is tailored to fit the needs of a generic drug that will protect against improper use, abuse, and diversion, which include the following multiple components: (1) product labeling; (2) strong educational initiatives in place and planned regarding the proper prescribing and clinical use of opioid analgesics as a class (though not specific to Oxycodone ER generic, these educational initiatives can be considered a component of the RMP since they will have a direct impact on appropriate use of the drug). Also, Endo is very much at the forefront of furthering the improvement of opioid prescribing by direct involvement in the development and validation of new clinical tools meant to assist physician assessment of patients' opioid abuse potential; (3) proactive surveillance methods in addition to tight oversight of the distribution chain along with no promotional or drug sales representative activities and (4) responsive interventions, including close working relationships with FDA and DEA.

Therefore, it is Endo's belief that this comprehensive RMP will protect the public and help minimize abuse, misuse, and diversion of its Oxycodone ER generic.

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2. PRODUCT LABELING

As required by the FD& C Act (505(j)(2)(A)(v)) and 21 CFR (314.94 (a)(8)(iv)), the Oxycodone ER generic product labeling will be identical to the reference listed drug's currently approved labeling (OxyContin®) (see Appendix 1). This label has the identical wording to OxyContin®'s "*Black Box Warning*," "*Warning*," "*Drug Abuse and Addiction*," and "*Precautions*" sections.

Additionally, a Patient Package Insert is part of the approved product labeling for the RLD. Therefore, Endo has submitted an identical Patient Package Insert as part of the approved labeling for Oxycodone ER generic. The Patient Package Insert translates the Package Insert into terms understandable by a typical patient (approximately a sixth grade level) (see Appendix 2).

3. EDUCATION

Since Endo will not be promoting nor marketing Oxycodone ER generic to physicians, no specific educational initiatives have or will be developed specifically for the product. However, Endo has and will continue to fund, develop, and implement a significant number of educational initiatives for physicians, pharmacists, nurses, and other allied healthcare professionals, as well as patients and their families, with the objective to educate them on the appropriate use of opioid analgesics, with a special emphasis on modified-release opioid products. In addition, Endo has plans to increase its educational initiatives aimed at those constituents who will be directly affected by the availability of Oxycodone ER generic- pharmacists and patients.

In general, Endo opioid educational programs aim to teach these audiences how to appropriately prescribe and/or use opioid analgesics. Teaching objectives of these programs most often include:

- Minimizing the risk of accidental exposure
- Identification of appropriate patient selection for opioid therapy
- Proper dosing for opioid initiation, titration and maintenance, opioid conversion, and tapering/discontinuation
- Minimizing risk for abuse and misuse

A sampling of Endo-sponsored patient and professional opioid educational programs is listed below.

3.1 Patient Education

3.1.1 Patient and Family Brochure: "Understanding Your Pain: Taking Oral Opioid Analgesics"

This patient education brochure was developed by Russell Portenoy, MD, Chris Pasero, RN, and Margo McCaffery, RN via an unrestricted educational grant. The brochure is intended to be provided to physicians and pharmacists for their patients being considered for or currently taking oral opioid analgesic therapy.

The brochure provides information to patients and family members on: opioid analgesics; their role in pain management; their potential side effects; the potential for addiction in patients taking

opioids for the management of pain; and patient information on how to take their medication and track their pain. The booklet will be disseminated broadly through the Endo sales force, the Scientific Affairs Department and the Endo corporate website, as well as at professional society meetings and educational conferences, including national pharmacist meetings such as the American Society of Health System Pharmacists, the Academy of Managed Care Pharmacy, and the American Society of Consultant Pharmacists. The brochure will be available in both print and electronic versions in 2Q 2004.

3.1.2 Pain Assessment Inventory and Patient/Family Education Materials

For the past four years, Endo has provided tear pads, which include the Brief Pain Inventory (BPI) and accompanying educational information on pain and pain assessment to physicians for their use in educating patients.

Upon publication of the national standards for pain assessment and management by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), Endo supported the development of another patient/family education brochure entitled "Understanding Your Pain." This brochure, developed through an unrestricted educational grant, was authored by Margo McCaffery, RN, Chris Pasero, RN, and edited by Russell Portenoy, MD. The brochure was endorsed by the JCAHO and has been distributed since 2001 in both print and electronic versions under the joint logo of JCAHO and Endo Pharmaceuticals.

During 2004, Endo plans to develop and disseminate additional patient/family education pieces such as the aforementioned brochure on opioid analgesics. In addition, Endo will continue to support the development and distribution of patient/family education materials through national patient organizations such as the American Pain Foundation, the National Pain Foundation and the American Chronic Pain Association.

3.1.3 Patient Package Insert

As part of the approved labeling for the Oxycodone ER generic, Endo has submitted a Patient Package Insert, which is identical to the approved product labeling for the RLD. The Patient Package Insert translates the Package Insert into terms understandable by a typical patient (approximately a sixth grade level) (see Appendix 2).

3.2 Professional Education

3.2.1 National Initiative on Pain Control (NIPC)

The "National Initiative on Pain Control" is a CME-accredited educational program solely supported by Endo Pharmaceuticals, which was established to advance clinicians' understanding of pain assessment/treatment, and to improve outcomes for patients with chronic pain. These programs are based upon a common slide kit developed by the NIPC Education Council, an educational advisory group of thought leaders in the area of pain management who are solely responsible for curriculum content and development. Once the curriculum has been developed, a core group of faculty is trained by the Education Council and the CME sponsor to deliver the programs. The faculty consists of physicians, nurses and pharmacists with an established expertise in the diagnosis and treatment of chronic pain.

The intended audience for the NIPC initiatives includes 60,000 internists, family physicians, osteopathic medicine specialists, general neurologists, physical medicine & rehab specialists, and other clinicians who manage patients with chronic pain.

To date, two live-CME modules, which specifically address the responsible prescribing of opioid analgesics, have been developed for the NIPC curriculum:

- "Advances in Opioid Analgesia: Maximizing Benefit; Minimizing Harm"
- "Opioid Analgesia: Practical Treatment of the Patient with Chronic Pain"

In addition, an audioconference module has been developed to extend the reach of the educational initiatives:

- "Opioid Analgesia: Enhancing Pain Management and Patient Outcomes"

This module can also be utilized in rural or difficult to access geographies, or in targeted interventional areas.

The NIPC programs have been supported through an unrestricted educational grant from Endo Pharmaceuticals since the initiative's inception in 2001; (Endo is the sole grantor supporting the NIPC and plans to continue grant support for NIPC indefinitely). For 2004, the opioid educational initiatives will be offered via various educational media such as:

- CME-accredited Dinner Dialogue™ Programs
- CME-accredited Audiconferences
- CME-accredited half-day symposia
- CME-accredited newsletters
- CME-accredited Webcasts

During 2004, these programs will educate clinicians nationwide on proper patient assessment, selection, and follow-up with regards to the use of modified-release opioids for the treatment of chronic pain. In addition, Endo has suggested to the CE provider that programs specifically relevant to pharmacists be added to the curriculum.

Specific materials, which have been developed, to date for the NIPC opioid analgesic modules include:

3.2.1.1 NIPC Core Curriculum/Faculty Guide

The NIPC core curriculum/faculty guide consists of all core curriculum slides, speaker notes, and references utilized by the NIPC visiting faculty. It describes the learning objectives, which must be met, a review of the ACCME requirements, as well as the curriculum materials and references.

3.2.1.2 NIPC Participant Guide

Provided to every participant in the live CME-accredited lectures and symposia. Purpose is to reiterate the CME learning objectives, to provide hard copies of the core curriculum slides, and to provide space for participants to record notes on the faculty presentations. Each participant guide also contains a copy of the CDROM resource kit, which the clinician can utilize to improve patient management.

3.2.1.3 NIPC Audioconference Guide

Provided to all registrants in the interactive audio conferences. The Audioconference Guide provides a means for the participants to view the core curriculum slides at their desks, while participating in the interactive audioconference. Each audioconference guide also contains a copy of the CDROM clinician resource kit.

3.2.1.4 NIPC Pain Management Today Newsletter

The NIPC ***Pain Management Today*** newsletter is a 16-page CME-accredited publication distributed bi-annually to 60,000 physicians who manage chronic pain patients. The publication is intended as a resource, which provides timely articles of clinical importance, patient assessment/management resources, case studies, and a clinical Q&A forum on chronic pain.

3.2.2 The Office of Women's Health of the US Department of Health & Human Services "Breakthroughs & Challenges in the Management of Common Chronic Pain Disorders" Initiative

This is a national CME-accredited initiative presented by the Office of Women's Health (OWH) Department of Health and Human Services (HHS), and chaired by Richard Payne, MD and Christine Miaskowski, RN, PhD, two nationally-recognized experts in the field of pain management and opioid analgesics.

The initiative will consist of a 3 day faculty meeting to discuss the most recent advances in managing chronic pain, followed by the development of a slide curriculum and series of enduring materials, which will be disseminated under the auspices of OWH/HHS and various national professional societies. A substantial portion of the curriculum will be focused on the responsible use of opioid analgesics for chronic pain disorders, including clinical and risk management considerations. The target audience for the educational materials will include family physicians, internists, neurologists, anesthesiologists, physical medicine & rehab, and other clinicians who treat chronic pain. This project is currently in early stages of development, with the initial faculty meeting scheduled for April 2004 and the first enduring material planned for 3Q 2004.

3.2.3 Satellite Symposia & Initiatives in Collaboration with Professional Societies

Endo recognizes the importance of peer-to-peer education via national congresses and professional societies as a means of advancing clinicians' knowledge about the responsible prescribing of opioid analgesics. To this end, Endo will support satellite symposia and educational programs in conjunction with professional congresses or societies such as:

- American College of Physicians
- American Academy of Family Physicians
- Society of Teachers of Family Medicine

- American Pain Society
- American Academy of Pain Medicine
- American Academy of Pain Management
- American Society of Addiction Medicine
- Annual Conference on Pain & Chemical Dependency
- PriMed Primary Care Regional Education Conferences
- Multi-National Association for Supportive Care in Cancer
- American Society of Pain Management Nurses
- Oncology Nursing Society
- American Society of Health System Pharmacists
- Academy of Managed Care Pharmacy
- Other regional pain education symposia

These symposia and initiatives are scheduled in conjunction with the above-listed Congresses, and/or professional society meetings.

3.2.4 Physician-in-Training and Primary Care Initiatives

Endo strongly believes in the need to educate physicians-in-training and primary care physicians on appropriate pain assessment, responsible prescribing of opioid analgesics, and appropriate patient follow-up which optimizes pain relief while minimizing the potential for adverse events, including medication misuse.

The following programs, supported through unrestricted educational grants from Endo, focus on these key groups of clinicians:

- APS Residents Course – an annual 2-day course taught to approximately 100 residents from family medicine, internal medicine, neurology, anesthesiology, physical medicine/rehab, and emergency medicine. Several hours of the course focus on opioid-related issues including: appropriate patient selection, practical prescribing considerations, side effects, patient follow-up and documentation, and addiction/dependence/abuse/diversion issues. Endo initiated this course 3 years ago and has been the sole supporter for the course every year since via an unrestricted educational grant to Northshore/Long Island Jewish Health System. This Course takes place annually immediately prior to the American Pain Society Meeting during the Spring.

- American Academy of Family Physicians – a 3-hour AAFP evidence-based CME video and educational monograph entitled "Managing Pain: Dispelling the Myths." This monograph, which has been distributed to all AAFP members, examines the appropriate assessment and management of pain, including: responsible use of opioid analgesics, discussion of controlled substances, abuse, addiction, pseudo-addiction, physical dependence, and tolerance.

- Society of Teachers of Family Medicine – for the past 2 years Endo has supported a full day pre-course at this annual meeting for family medicine faculty and residency program directors. The course, developed and presented by the STFM's Pain Management Interest Group, focuses on the essential principles and practice of pain assessment and management. A substantial amount of didactic and interactive discussion time is focused on the appropriate prescribing of opioid analgesics, clinical considerations, and abuse/misuse/addiction/diversion issues. This course will occur during 4 Q2004.

- California Primary Care Course – 12 hour CME-accredited course developed to educate primary care physicians in California on the principles/practice of pain management, including several hours related to appropriate prescribing of opioid analgesics, appropriate patient selection, proper education and follow-up, and addiction/abuse/diversion issues. Endo was the sole grantor for this Course during 4Q 2003 and a second offering of the Course is planned for 3Q 2004.

- American College of Physicians – 3-hour workshop on Pain Management at the national ACP meeting. A substantial portion of this workshop for internists focuses on the appropriate use of opioid analgesics, patient selection and follow-up, and addiction/abuse/diversion issues. This Workshop will take place during 1Q 2004.

- PriMed West Regional Conference – 2-hour symposium at this annual meeting of primary care physicians to occur 2Q 2004. 50% of the program will be devoted to appropriate prescribing of opioid analgesics, as well as side effects and the potential for misuse/diversion. Following the conference, CME-accredited enduring materials will be developed for distribution to primary care physicians via state academies of family medicine.

3.2.5 *www.PainEdu.org* Website and Manual

This initiative consists of a website and pocket manual created by Inflexxion, a multimedia-based technology company specializing in the development and delivery of scientifically-based

behavioral health interventions. *PainEdu* utilizes nationally-recognized experts within the behavioral health, oncology, pain medicine and addiction medicine fields to develop content for both the website and the pocket manual.

The website, which includes interactive case-based learning, interviews with experts, resource materials/links, and the Clinical Companion manual, is accredited for continuing medical, pharmacy, nursing, and psychology education. Endo has supported the development of and continual updates to *PainEdu* through an unrestricted educational grant.

3.2.6 ACPE-Accredited Pharmacy Education Monograph

Endo will utilize customized ACPE-accredited monographs to educate pharmacists on the proper role of modified-release opioid analgesics for the treatment of chronic pain. These educational materials will discuss the clinical/risk management considerations, and will stress the importance of the relationship between the prescribing physician and the pharmacist. The monographs will be distributed to all pharmacy specialties, including retail independent, retail chain, consultant pharmacists, hospital pharmacists, and HMO-based pharmacists via national pharmacy practice publications. The accredited program will also be available for 2 years on the publication's website. This initiative's materials will be available by 3Q 2004.

3.2.7 "Practitioner's Guide to Prescribing Opioid Analgesics for Persistent Pain" Handbook

This practical clinical handbook is authored by Russell Portenoy, MD and Perry Fine, MD, two nationally-recognized experts on opioid analgesics, and will be published by McGraw Hill. The handbook, which will be made available both directly from Endo and via professional society meetings, is intended to provide the essential information necessary for physicians to responsibly prescribe opioid analgesics for persistent pain, including both clinical and risk management considerations. The handbook development and dissemination is being supported through an unrestricted educational grant from Endo and is planned to become available by mid-2004.

3.2.8 "Advances in Cancer Pain: A Bedside Approach" Handbook

This handbook, authored by Ann Berger, RN, MD, Chief of Pain and Palliative Care Service at the National Institute of Health, and published by The Oncology Group, is intended to provide practical, clinical information on the assessment and treatment of cancer pain. The handbook will be distributed to both primary care clinicians and oncology specialists/nurses via an

unrestricted educational grant from Endo. At least half of the handbook will focus on the appropriate prescribing of opioid analgesics, including both clinical and risk management issues, and will become available during 3Q 2004.

3.2.9 AAPM/APS Consensus Statement on the Use of Opioids for the Treatment of Chronic Pain

This joint consensus statement was prepared by the American Academy of Pain Medicine (AAPM) and the American Pain Society (APS) to provide guidance to clinicians on the undertreatment of pain; to provide clarity on issues of addiction, diversion, tolerance, and side effects; and to promulgate principles of good medical practice with regards to the use of opioid analgesics for chronic pain. Endo has purchased quantities of the Consensus Statement to distribute through its Scientific Affairs/Medical Information Departments, as well at national medical and pharmacy meetings via Endo's Scientific Resource Center booth.

3.3 Development of New Clinically Useful Validated Tools

3.3.1 Screener and Opiate Assessment for Patients With Pain (SOAPP)

Endo is currently supporting and will continue to support the development of what is referred to as the SOAPP tool – a prospective, self-report screening tool funded by grants from NIDA and the National Institutes of Health (NIH), and developed by a team from Harvard University, Brigham and Women's Hospital, and Inflexxion, a consulting company with expertise in development of screening tools. Inflexxion will develop the screening tool under the auspices of a NIDA/NIH grant, with input and review by a scientific advisory group of national pain medicine and substance abuse experts.

The SOAPP tool is a brief screening, self-report tool for those chronic pain patients being considered for opioid therapy. It will be easily completed and scored in less than 10 minutes in the waiting room of a physician's office or alternatively could be completed prior to the visit either as a brief paper questionnaire, online, or through an Interactive Voice Recognition (IVR) system. Such a tool could help classify patients along a continuum of greater or lesser likelihood of encountering problems during a regimen of opioid medications. This information, along with interpretive cutoffs, would inform the healthcare provider that a given patient may require extra monitoring while on pain medications, or perhaps, additional or alternative treatments should be considered.

A rigorous, methodological approach to establish reliability and predictive validity of the SOAPP screening tool is being used. Accepted principles of test-construction are being followed to develop a self-report questionnaire for persons with chronic pain who are considered candidates for long-term opioid therapy. A body of literature is being used to establish those domains and markers that correlate with potential for addiction/abuse, and focus groups of chronic pain patients, pain and addiction specialists, and primary care clinicians are providing input into the generation of items for the SOAPP. This process will result in a substantial pool of items. This pool of items will undergo two reviews for quality by the research staff at Brigham and Women's Hospital/Harvard Medical School and the scientific advisory group in order to begin the process of deleting poorly-predictive items. The resulting pool of items will form the body of an alpha version of the SOAPP tool, referred to as SOAPP Version 1 (SOAPP V1).

Whereas, the final version of the SOAPP will be empirically-derived from prospectively testing those patients who may go on to have a difficulty with opioids, SOAPP V1 is based on expert opinion, thorough literature reviews, and current best practices with regard to screening for abuse potential. Thus, the SOAPP V1, upon its completion in 1Q 2004, will represent the best available screening/risk reduction approaches for those patients with chronic pain who are being considered for long-term opioid therapy.

The SOAPP V1will then be tested using respondents who are chronic pain patients (1) on opioid therapy, (2) not on opioid therapy, (3) without substance abuse history, and (4) with substance abuse history. Surviving items will form a beta version of the SOAPP tool and be subjected to further testing/validation. External data will help to establish the predictive validity of items in a larger, follow-up evaluation including (1) urine toxicology screen results, (2) spouse reports, (3) treating physician responses, (4) pain severity measures, and (5) independent psychological interviews. Analyses will be conducted to determine those items that are most predictive of substance abuse validity and reliability. These items will constitute the final SOAPP tool.

3.3.2 Design, Testing and Diffusion of SOAPP Delivery Systems

The concepts and practice of what has been called 'The Theory of Diffusion of Innovation' will be used to achieve rapid dissemination and utilization of the SOAPP tool once it is completed. This work, which is being supported through an unrestricted educational grant from Endo, entails the following elements:

- Studies of the possible delivery modalities for SOAPP. Potential vehicles for delivery include: paper and pencil questionnaire, Palm Pilot technology, IVR, interactive kiosks, etc.

- Studies of current practice patterns: these would be naturalistic, observational studies of how physicians/nurses currently follow and screen their chronic pain patients.
- Focus group studies with physicians, nurses and chronic pain patients in order to determine how they would use the SOAPP were it delivered through various modalities.
- Studies with the prototyped SOAPP V1 tool. While it will not yet have undergone complete psychometric testing, it will constitute the best approximation of what the major items and elements of the final SOAPP tool would be. SOAPP V1 will be tested using various delivery mechanisms and process strategies for inclusion of the SOAPP as a standard of practice in treating chronic pain patients.

The goal of all of the elements described above would be to create a tool that, once it is completed and empirically tested with NIDA/NIH support, would be immediately usable and integrated into practice by physicians around the country.

4. SURVEILLANCE

4.1 Pharmacovigilance

4.1.1 Postmarketing Surveillance

The Global Safety & Pharmacovigilance Department of Endo will conduct proactive surveillance of all oxycodone products (brand and generic extended-release and immediate-release formulations) adverse event reports received via post-marketing surveillance (spontaneous reports, scientific literature, post-marketing clinical investigations, and post-marketing epidemiological surveillance studies). Endo will review, investigate, process, and track adverse events for safety surveillance and safety signal detection.

Reports of all serious adverse events sent to the FDA will be made in accordance with the current Federal Regulations. In addition, Endo will send, for a period of 2 years from the date of launch, adverse event reports of misuse, abuse, dependence, diversion, overdose, death, and unexplained death with the use of Oxycodone ER in an expedited manner (15-day Alert), whether or not the experience is unexpected according to the approved labeling.

4.1.2 Periodic Reports

Endo will assemble and submit periodic reports for all adverse events received for Oxycodone ER in accordance with current Federal Regulations. The periodic reports will be submitted on a quarterly basis for the first three years of marketing and yearly thereafter. These reports will be reviewed by Endo's Safety Review Board for trending and signal detection, specifically for increased reports of abuse, misuse or overdose (see Section 4.2).

4.1.3 Secondary Databases

4.1.3.1 Toxic Exposure Surveillance System (TESS)

Toxic Exposure Surveillance System (TESS) data are compiled by the American Association of Poison Control Centers (AAPCC) in cooperation with the majority of US poison centers. These data are used to identify hazards early, focus prevention education, guide clinical research, and direct training. TESS data have prompted product re-formulations, repackaging, recalls, and bans; are used to support regulatory actions; and form the basis of post-marketing surveillance of newly released drugs and products. Endo will monitor all oxycodone products (brand and generic, extended-release and immediate-release formulations), exposures in the AAPCC annual report, which is published annually. These exposures will be treated as adverse event reports and will be followed up with the individual Poison Control Center for submission to the FDA either on an expedited manner or in the periodic reports. Endo will look for trends in increased abuse of the product. If identified, FDA will be notified and intervention will be initiated (see Section 5.1).

4.1.3.2 Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network (DAWN) is a national surveillance system that monitors trends in drug-related emergency department visits and deaths. DAWN is operated by the Substance Abuse and Mental Health Services Administration (SAMHSA), of the U.S. Department of Health and Human Services. DAWN provides semiannual estimates of the number of drug-related visits to hospital emergency departments based on a nationally representative sample (21 metropolitan areas) of short-stay general hospitals located throughout the coterminous United States. DAWN also provides counts of drug-related deaths from 128 medical examiners and coroners (ME/Cs) in 42 metropolitan areas, which is published annually. Endo will monitor the DAWN reports, when released, to identify geographic trends, which may not be identified through standard post-marketing surveillance. The Agency will be

notified if any area of increased activity is identified for any marketed formulation of Oxycodone and Endo will initiate targeted education initiatives in the geographic region.

4.1.3.3 FDA's Freedom of Information

Endo has a licensing agreement with DrugLogic to view safety data on all pharmaceutical products, which are received by DrugLogic from FDA under the Freedom of Information Act. DrugLogic provides information regarding the number of adverse events received for other marketed products. Oxycodone adverse event information for all marketed formulations that has been obtained via post marketing surveillance will be compared to other products of potential abuse, in this therapeutic class via DrugLogic data. Endo will use DrugLogic's Proportion Analysis Engine to look for deviations in reaction frequency for Oxycodone ER compared to an expected value derived from a background set of drugs (e.g., comparing Oxycodone ER to other opioid products, such as fentanyl and morphine).

4.1.3.4 Media Screening

In addition to reviewing the medical literature on a continual basis, Endo will subscribe to a media screening service which will review the lay press for articles pertaining to opioid abuse, with specific searches regarding "Oxycodone ER" and "Oxycontin®." This search will be performed regularly with a report generated at least monthly. If areas of increased media coverage regarding abuse or diversion of the product are identified further investigation will be undertaken and targeted educational initiatives will be implemented as warranted.

4.2 Endo Safety Review Board (ESRB)

Endo has an established Safety Review Board (ESRB) to review adverse events and identify new safety signals and trends for all Endo products. The ESRB will review aggregate adverse event data received for Oxycodone ER on a quarterly basis at a minimum with emphasis on events such as misuse, abuse, dependence, diversion, overdose, death, and unexplained death. However, if Endo identifies a trend or signal prior to the quarterly review, the ESRB will address these issues promptly and independently.

The ESRB is a multi-disciplinary team with representatives from Scientific Affairs, Medical Affairs, Clinical Operations, Regulatory Affairs, Project Management, Global Safety & Pharmacovigilance, and Pre-clinical Drug Safety (see Appendix 5, ESRB Standard Operating Procedure; Appendix 6, ESRB Member Biographies). The ESRB will review adverse event data

of Oxycodone ER/IR that have been collected as part of the post-marketing safety surveillance. As part of this surveillance, the ESRB will investigate and review all cases of clinical significance, misuse, abuse, dependence, diversion, overdose, death, and unexplained death to detect trends. Endo's review will include patient demographics, physician demographics, and information about the use of concomitant medications when available. These data will be used in conjunction with longitudinal prescribing databases. In addition, information obtained will be compared to other products of potential abuse in this therapeutic class. Once Endo has analyzed the information, if a trend is identified, the Agency will be notified and targeted education and safety measures will be initiated in the geographic area identified.

4.3 Risk Management Team

In addition to ESRB, a Risk Management Team has been formed at Endo, which will meet on a monthly basis to evaluate data collected from post-marketing surveillance, secondary databases, media screening, and IMS data. The team will be chaired by members of the Global Safety & Pharmacovigilance Department with representatives from the following disciplines: Operations (supply chain), Regulatory Affairs, Clinical Development & Education, Sales, and Marketing. The team will be responsible for longitudinal evaluation of all reports of misuse, abuse, dependence, diversion, overdose, death, and unexplained death received for Oxycodone products with the aim to identify trends and potential new safety signals, as well as develop and initiate targeted educational initiatives when warranted. These reports will be used in conjunction with IMS prescribing databases for geographic trending regarding the above-mentioned events. The team will be responsible for notifying the appropriate parties for intervention in the event a potential signal is identified (see Section 5.1).

4.4 Analysis of Surveillance Data

Utilizing the databases enumerated above, Endo will perform longitudinal tracking of all reports of misuse, abuse, dependence, diversion, overdose, death, and unexplained death received for oxycodone ER and oxycodone IR products. In addition, Endo will track changes in prescribing practices using longitudinal prescribing databases, such as IMS, on a monthly basis to identify geographic trends. Finally, Endo will send an analysis of these findings from the surveillance data to the Agency on a semiannual basis.

4.5 Oversight of the Distribution Chain

As for all of Endo's controlled substance products, the manufacturing and distribution chain is highly controlled and closely monitored. Endo employs sophisticated controls and monitoring at its manufacturing sites, in transit to Endo's distribution center, at the distribution center, and in transit to the wholesalers and large retail chains with appropriate CII vaults. All of Endo's manufacturing and distribution sites are rigorously inspected by the Drug Enforcement Agency (DEA) and all have close working relationships with their respective law enforcement agencies.

Endo's oversight includes physical and administrative controls as well as significant monitoring activities. Endo's physical and administrative controls at the manufacturers and distribution sites meet or exceed DEA requirements for CII materials. Endo's typical manufacturing and distribution chain controls are shown in Appendix 3; order management practices are presented in Appendix 4. Detection techniques, such as undercover security personnel and random checks, are employed in many cases. In addition, order management and transaction data are monitored frequently to look for unusual changes in deliveries to customers. For example, order and delivery discrepancies are tracked weekly and trends identified where discernable. These discrepancies may include events such as shortages, damage, and late deliveries. When trends are observed, actions are taken which may include changes in commercial carriers, personnel, outer packaging, and delivery schedules. Additional monitoring of specific or anonymous complaints is performed through Endo's external website and customer service email address.

4.6 No Promotional Activity / No Drug Sales Representative Detailing Activity

Oxycodone ER generic's customers are retail pharmacy chains, wholesale distributors, and institutional buyers, not physicians. Therefore, Endo will not have any promotional activity to physicians, drug sales representative detailing activity, nor journal and other drug advertising to doctors for Oxycodone ER generic. Thus, these areas of potential sources of risk are not present for this drug product.

5. INTERVENTION

5.1 Risk Intervention

As per Endo's overall opioid RMP, if Endo identifies any geographical areas of significant increases of abuse, misuse, or overdose with any of its opioids, including Oxycodone ER

generic, Endo will take immediate and appropriate action, the specifics of which will depend upon the circumstances. Possible scenarios include:

- Diversion is suspected in distribution chain:
  - Endo will immediately alert the established security and management contacts at the manufacturing and distribution sites that may potentially be involved. These sites will aggressively investigate and search for possible diversion activities and will involve local DEA and law enforcement organizations as actionable details are discovered.
- Significant increase in cases of misuse, abuse, dependence, overdose, death, or unexplained death identified in specific geographic region by Risk Management Team:
  - Focused educational initiatives to targeted geographic area, which may be targeted towards health care providers, pharmacists, and/or the community.
- Suspected unscrupulous medical professionals prescribing large amounts of drug to non-patients (e.g., "pill mill") identified via IMS data:
  - Refer name to DEA for possible investigation.
- Localized area of local pharmacy thefts:
  - Focused educational initiatives to targeted geographic area, which may be targeted towards health care providers, pharmacists, and/or the community.

5.2 Close Working Relationships with Government Agencies and Officials

Endo has a history of working closely with the FDA and DEA on many issues that relate to its marketed products and will continue such a relationship with regards to Oxycodone ER generic. Endo will also work closely with other government agencies and officials wherever appropriate to minimize diversion, misuse, and abuse of Oxycodone ER generic.

6. CONCLUSION

Endo Pharmaceuticals Inc. is a pharmaceutical company focused on improving the care of pain patients through the development of alternative analgesics. Oxycodone ER generic will offer an affordable alternative to OxyContin®, a drug which physicians and patients have found to be a very effective medication for the treatment of moderate to severe chronic pain. Endo understands the potential risks inherent in Oxycodone ER generic and thus has developed a RMP tailored to meet the needs of a generic drug that will not be promoted, advertised, or sold directly

to physicians. This comprehensive RMP has multiple components that can effectively minimize the risk of abuse, misuse and diversion of a generic modified-release opioid.

APPENDIX 1 – OXYCODONE ER LABELING

Oxycodone hydrochloride extended-release tablets
10 mg, 20 mg, 40 mg

CII

R_x only

WARNING:

Oxycodone hydrochloride extended-release tablets are an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

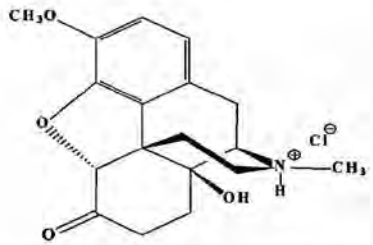
Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Oxycodone hydrochloride extended-release tablets are NOT intended for use as a prn analgesic.

Oxycodone hydrochloride extended-release tablets ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

Oxycodone hydrochloride extended-release tablets are an opioid analgesic supplied in 10 mg, 20 mg and 40 mg tablet strengths for oral administration. The tablet strength describes the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.82

The chemical formula is 4, 5-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio methacrylate copolymer, colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium hydroxide, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, stearic acid, and titanium dioxide. In addition, the 10 mg tablet contains polysorbate 80, the 20 mg tablet also contains FD&C Red #40, FD&C Yellow #6, polydextrose, and triacetin, and the 40 mg tablet also contains iron oxide red, iron oxide yellow, and polysorbate 80.

CLINICAL PHARMACOLOGY

Central Nervous System

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic affect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone hydrochloride extended-release tablet overdose (see **OVERDOSAGE**).

Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration – Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall "drug effect," analgesia and feelings of "relaxation."

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients need to be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration – Adverse Experience Relationships

Oxycodone hydrochloride extended-release tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as

nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see **DOSAGE AND ADMINISTRATION**), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

PHARMACOKINETICS AND METABOLISM

The activity of oxycodone hydrochloride extended-release tablets is primarily due to the parent drug oxycodone. Oxycodone hydrochloride extended-release tablets are designed to provide controlled delivery of oxycodone over 12 hours.

Breaking, chewing or crushing oxycodone hydrochloride extended-release tablets eliminates the controlled delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

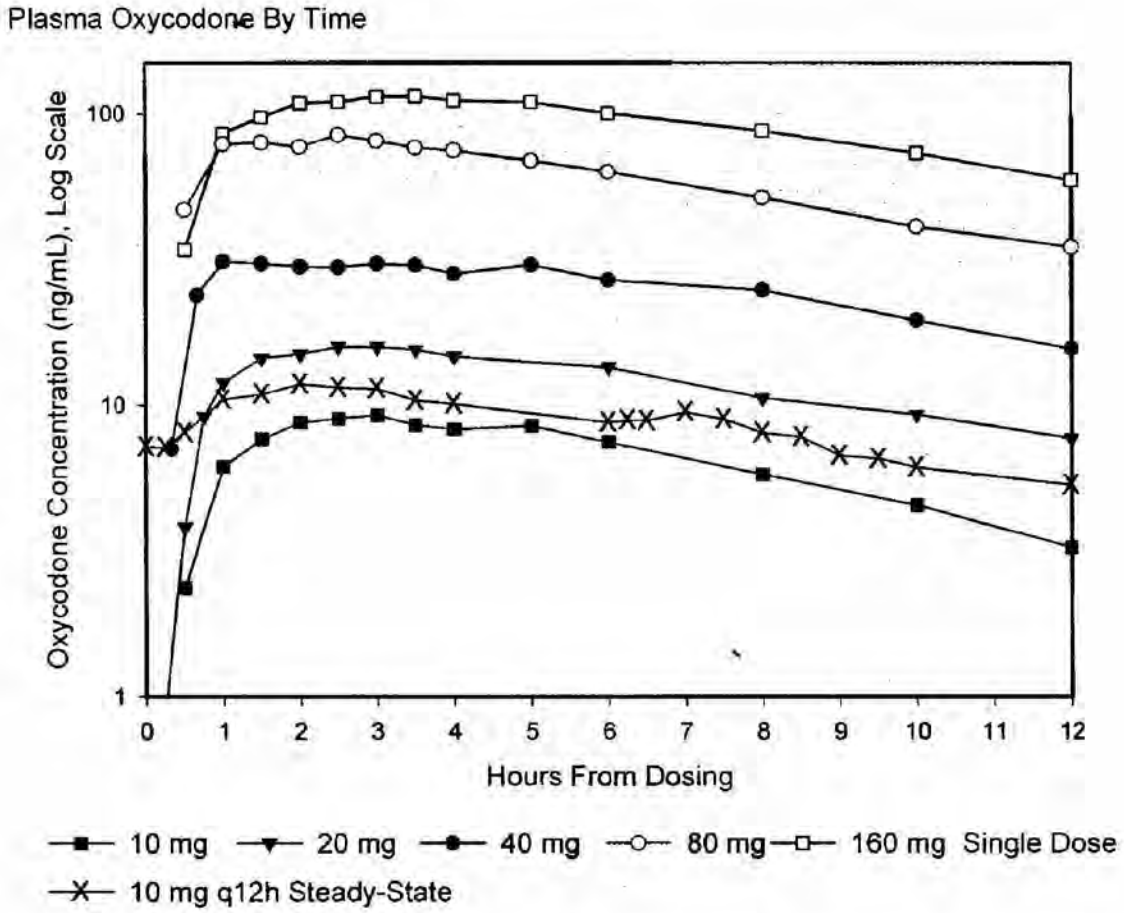
Oxycodone release from oxycodone hydrochloride extended-release tablets is pH independent. Oxycodone is well absorbed from oxycodone hydrochloride extended-release tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of oxycodone hydrochloride extended-release tablets to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Dose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of oxycodone hydrochloride extended-release tablets was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers, the t½ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, oxycodone hydrochloride extended-release tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Another study established that the 160 mg tablet is bioequivalent to 2 x 80 mg tablets as well as to 4 x 40 mg for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 2 below). Given the short half-life of elimination of oxycodone from

oxycodone hydrochloride extended-release tablets, steady-state plasma concentrations of oxycodone



are achieved within 24-36 hours of initiation of dosing with oxycodone hydrochloride extended-release tablets. In a study comparing 10 mg of oxycodone hydrochloride extended-release tablets every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the oxycodone hydrochloride extended-release tablets than for the immediate-release formulation.

Table 1
Mean [% coefficient variation]

Regimen	Dosage Form	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg oxycodone hydrochloride extended-release tablets	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg oxycodone hydrochloride extended-release tablets	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg oxycodone hydrochloride extended-release tablets	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg oxycodone hydrochloride extended-release tablets*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a
Multiple Dose	10 mg oxycodone hydrochloride extended-release tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

Table 2

Mean [% coefficient variation]

Regimen	Dosage Form	AUC∞ (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
• Single Dose	4 x 40 mg oxycodone hydrochloride extended-release tablets*	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
	2 x 80 mg oxycodone hydrochloride extended-release tablets*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a
	1 x 160 mg oxycodone hydrochloride extended-release tablets*	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

† for single-dose AUC = AUC_{0-inf}; for multiple dose AUC = AUC_{0-T}
* data obtained while volunteers received naltrexone which can enhance absorption.

Oxycodone hydrochloride extended-release tablets ARE NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that oxycodone hydrochloride extended-release tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from oxycodone hydrochloride extended-release tablets. However, the peak plasma concentration of oxycodone increased by 25% when oxycodone hydrochloride extended-release 160 mg tablet was administered with a high fat meal.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen and brain. Oxycodone has been found in breast milk (see **PRECAUTIONS**).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see **Drug-Drug Interactions**).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects,

respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in t½ of elimination for oxycodone of only 1 hour (see **PRECAUTIONS**).

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The t½ elimination for oxycodone increased by 2.3 hours (see **PRECAUTIONS**).

Drug-Drug Interactions (see **PRECAUTIONS**)

Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic anti-depressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.

Pharmacodynamics

A single-dose, double-blind, placebo- and dose-controlled study was conducted using oxycodone hydrochloride extended-release tablets (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. Twenty and 30 mg of oxycodone hydrochloride extended-release tablets were superior in reducing pain compared with placebo, and this difference was statistically significant. The onset of analgesic action with oxycodone hydrochloride extended-release tablets occurred within 1 hour in most patients following oral administration.

CLINICAL TRIALS

A double-blind placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with chronic, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, 20 mg oxycodone hydrochloride extended-release tablets q12h but not 10 mg oxycodone hydrochloride extended-release tablets q12h decreased pain compared with placebo, and this difference was statistically significant.

INDICATIONS AND USAGE

Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a

continuous, around-the-clock analgesic is needed for an extended period of time.

Oxycodone hydrochloride extended-release tablets are **NOT** intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the immediate post-operative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persists for an extended period of time. Oxycodone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

Oxycodone hydrochloride extended-release tablets are contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone hydrochloride extended-release tablets are contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Oxycodone hydrochloride extended-release tablets have been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

Oxycodone hydrochloride extended-release tablets are a mu-agonist opioid with an abuse liability similar to morphine and are a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Oxycodone hydrochloride extended-release tablets, like other opioids, have been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Oxycodone hydrochloride extended-release tablets consist of a polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in oxycodone hydrochloride extended-release tablets, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

Oxycodone hydrochloride extended-release tablets may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Hypotensive Effect

Oxycodone hydrochloride extended-release tablets may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine type,

should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of oxycodone hydrochloride extended-release tablets is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with Other CNS Depressants

Oxycodone hydrochloride extended-release tablets should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of oxycodone hydrochloride extended-release tablets.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Post-Operative Use

Oxycodone hydrochloride extended-release tablets are not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the

immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

Oxycodone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).

Patients who are already receiving oxycodone hydrochloride extended-release tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

Oxycodone hydrochloride extended-release tablets and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers

If clinically advisable, patients receiving oxycodone hydrochloride extended-release tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that oxycodone hydrochloride extended-release tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that oxycodone hydrochloride extended-release tablets were designed to work properly only if swallowed whole. Oxycodone hydrochloride extended-release tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of oxycodone hydrochloride extended-release tablets without consulting the prescribing professional.
5. Patients should be advised that oxycodone hydrochloride extended-release tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine oxycodone hydrochloride extended-release tablets with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that oxycodone hydrochloride extended-release tablets are a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that if they have been receiving treatment with oxycodone hydrochloride extended-release tablets for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the oxycodone hydrochloride extended-release tablets dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to

accomplish a gradual discontinuation of the medication.

10. Patients should be instructed to keep oxycodone hydrochloride extended-release tablets in a secure place out of the reach of children. When oxycodone hydrochloride extended-release tablets are no longer needed, the unused tablets should be destroyed by flushing down the toilet.

See text of Patient Package Insert, which appears after the **HOW SUPPLIED** section.

Use in Drug and Alcohol Addiction

Oxycodone hydrochloride extended-release tablets are an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including oxycodone hydrochloride extended-release tablets, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

Oxycodone hydrochloride extended-release tablets, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 mcg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 mcg/mL and with activation 48 hours after exposure at doses of up to 5000 mcg/mL, and in the *in vivo* bone

marrow micronucleus test in mice (at plasma levels of up to 48 mcg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 mcg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 mcg/mL or greater with metabolic activation and at 400 mcg/mL or greater without metabolic activation.

Pregnancy

Teratogenic Effects—Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Oxycodone hydrochloride extended-release tablets are not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving oxycodone hydrochloride extended-release tablets because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of oxycodone hydrochloride extended-release tablets have not been established in pediatric patients below the age of 18. **It must be remembered that oxycodone hydrochloride extended-release tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see **Pharmacokinetics and Metabolism**). Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride extended-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation

of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received oxycodone hydrochloride extended-release tablets. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to ½ of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of oxycodone hydrochloride extended-release tablets in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

The safety of oxycodone hydrochloride extended-release tablets was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received oxycodone hydrochloride extended-release tablets in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with oxycodone hydrochloride extended-release tablet therapy in clinical use are those observed with other opioid analgesics, including

respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with oxycodone hydrochloride extended-release tablets are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as oxycodone hydrochloride extended-release tablet therapy is continued and some degree of tolerance is developed.

Clinical trials comparing oxycodone hydrochloride extended-release tablets with immediate-release oxycodone and placebo revealed a similar adverse event profile between oxycodone hydrochloride extended-release tablets and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

Table 3

	Oxycodone Hydrochloride Extended-Release Tablets (n=227) (%)	Immediate-Release (n=225) (%)	Placebo (n=45) (%)
Constipation	23	26	7
Nausea	23	27	11
Somnolence	23	24	4
Dizziness	13	16	9
Pruritus	13	12	2
Vomiting	12	14	7
Headache	7	8	7
Dry Mouth	6	7	2
Asthenia	6	7	--
Sweating	5	6	2

The following adverse experiences were reported in oxycodone hydrochloride extended-release tablet treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in post marketing experience:

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

Urogenital: amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of oxycodone hydrochloride extended-release tablets, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when oxycodone hydrochloride extended-release tablets are abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive

measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including oxycodone hydrochloride extended-release tablets, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE.

OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain requiring treatment with a strong opioid for continuous, around-the-clock analgesia for an extended period of time. The extended-release nature of the formulation allows oxycodone hydrochloride extended-release tablets to be effectively administered every 12 hours (see **CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM**.) While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one

opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Health care professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring [See **BOXED WARNINGS**].

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

(1) The general condition and medical status of the patient;

(2) the daily dose, potency, and kind of the analgesic(s) the patient has been taking;

(3) the reliability of the conversion estimate used to calculate the dose of oxycodone;

(4) the patient's opioid exposure and opioid tolerance (if any);

(5) special safety issues associated with conversion to oxycodone hydrochloride extended-release tablet doses at or exceeding 160 mg; and

(6) the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of oxycodone hydrochloride extended-release tablets in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see **PRECAUTIONS: Drug-Drug Interactions**).

For initiation of oxycodone hydrochloride extended-release tablet therapy for patients previously taking opioids, the conversion ratios from Foley, KM. [NEJM, 1985; 313:84-95], found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

Experience indicates a reasonable starting dose of oxycodone hydrochloride extended-release tablets for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg q12h. If a non-opioid analgesic is being provided, it may be continued. Oxycodone hydrochloride extended-release tablets should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.

2. When converting from oxycodone, divide the 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of oxycodone hydrochloride extended-release tablets.

3. Round down to a dose which is appropriate for the tablet strengths available (10 mg, 20 mg, 40 mg, and 80 mg tablets).

4. Discontinue all other around-the-clock opioid drugs when oxycodone hydrochloride extended-release tablet therapy is initiated.

5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

Table 4

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*
(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	--
Codeine	0.15	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

***To be used only for conversion to oral oxycodone.** For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of a suitable short-acting analgesic.

Oxycodone hydrochloride extended-release tablets can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see **PRECAUTIONS**).

Conversion from Transdermal Fentanyl to Oxycodone Hydrochloride Extended-Release Tablets

Eighteen hours following the removal of the transdermal fentanyl patch, oxycodone hydrochloride extended-release tablet treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of oxycodone hydrochloride extended-release tablets, should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. The patient should be followed closely for early

titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid- naive, will experience side effects. Frequently the side effects from oxycodone hydrochloride extended-release tablets are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the health-care team, the patient and the caregiver/family.

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with oxycodone hydrochloride extended-release tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from Oxycodone Hydrochloride Extended-Release Tablets to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING

Oxycodone hydrochloride extended-release tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

Oxycodone hydrochloride extended-release tablets have been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

Oxycodone hydrochloride extended-release tablets are supplied as follows:

10 mg
Unscored, coated, round,
white tablet, imprinted
with "E702" on one side
and "10" on the other.
Bottles of 30 with a child-resistant closure
NDC 60951-702-30
Bottles of 500 with a child-resistant closure
NDC 60951-702-85

20 mg
Unscored, coated, round,
pink tablet, imprinted
with "E703" on one side
and "20" on the other.
Bottles of 30 with a child-resistant closure
NDC 60951-703-30
Bottles of 500 with a child-resistant closure
NDC 60951-703-85
40 mg
Unscored, coated, round, yellow tablet, imprinted with "E705" on one side and "40" on the other.
Bottles of 30 with a child-resistant closure
NDC 60951-705-30
Bottles of 500
NDC 60951-705-85

Desiccant enclosed in all bottles.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure (as required).

CAUTION

DEA Order Form Required.

ENDO PHARMACEUTICALS

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317

Printed in U.S.A.

412542/February, 2003

PATIENT INFORMATION

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS CII

Oxycodone Hydrochloride Extended-Release Tablets, 10 mg
Oxycodone Hydrochloride Extended-Release Tablets, 20 mg
Oxycodone Hydrochloride Extended-Release Tablets, 40 mg

Rx only

Read this information carefully before you take Oxycodone Hydrochloride Extended-Release Tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if Oxycodone Hydrochloride Extended-Release Tablets are right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information I Should Know About Oxycodone Hydrochloride Extended-Release Tablets?

- **Use Oxycodone Hydrochloride Extended-Release Tablets the way your doctor tells you to.**
- **Use Oxycodone Hydrochloride Extended-Release Tablets only for the condition for which it was prescribed.**
- **Oxycodone Hydrochloride Extended-Release Tablets are not for occasional ("as needed") use.**
- **Swallow the tablets whole.** Do not break, crush, dissolve, or chew them before swallowing. Oxycodone Hydrochloride Extended-Release Tablets work properly over 12 hours only when swallowed whole. **If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.**
- **Keep Oxycodone Hydrochloride Extended-Release Tablets out of the reach of children.** Accidental overdose by a child is dangerous and may result in death.
- **Prevent theft and misuse.** Oxycodone Hydrochloride Extended-Release Tablets contain a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What are Oxycodone Hydrochloride Extended-Release Tablets?

Oxycodone Hydrochloride Extended-Release Tablets are tablets that come in several strengths and contain the medicine oxycodone (ox-e-KOE-done). This medicine is a painkiller like morphine. Oxycodone Hydrochloride Extended-Release Tablets treat moderate to severe pain that is expected to last for an extended period of time. Use Oxycodone Hydrochloride Extended-Release Tablets regularly during treatment. They contain enough medicine to last for up to twelve hours.

Who Should Not Take Oxycodone Hydrochloride Extended-Release Tablets?

Do not take Oxycodone Hydrochloride Extended-Release Tablets if

- your doctor did not prescribe Oxycodone Hydrochloride Extended-Release Tablets for you.
- your pain is mild or will go away in a few days.
- your pain can be controlled by occasional use of other painkillers.
- you have severe asthma or severe lung problems.
- you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox, Tylenol with Codeine, or Vicodin). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
- you had surgery less than 12 – 24 hours ago and you were not taking Oxycodone Hydrochloride Extended-Release Tablets just before surgery.

Your doctor should know about all your medical conditions before deciding if Oxycodone Hydrochloride Extended-Release Tablets are right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking Oxycodone Hydrochloride Extended-Release Tablets.

If you are pregnant or plan to become pregnant, talk with your doctor. Oxycodone Hydrochloride Extended-Release Tablets may not be right for you. **Tell your doctor if you are breast feeding.** Oxycodone Hydrochloride Extended-Release Tablets will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with Oxycodone Hydrochloride Extended-Release Tablets, especially if they cause drowsiness.

How Should I Take Oxycodone Hydrochloride Extended-Release Tablets?

- **Follow your doctor's directions exactly.** Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take Oxycodone Hydrochloride Extended-Release Tablets more often than prescribed.
- **Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.**
- **If you miss a dose,** take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.
- **In case of overdose,** call your local emergency number or poison control center right away.
- **Review your pain regularly with your doctor** to determine if you still need Oxycodone Hydrochloride Extended-Release Tablets.

If you continue to have pain or bothersome side effects, call your doctor.

Stopping Oxycodone Hydrochloride Extended-Release Tablets. Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking Oxycodone Hydrochloride Extended-Release Tablets all at once if you have been taking it for more than a few days.

After you stop taking Oxycodone Hydrochloride Extended-Release Tablets, flush the unused tablets down the toilet.

What Should I Avoid While Taking Oxycodone Hydrochloride Extended-Release Tablets?

- **Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities** until you know how you react to this medicine. Oxycodone Hydrochloride Extended-Release Tablets can make you sleepy.
- **Do not drink alcohol while using Oxycodone Hydrochloride Extended-Release Tablets. It may increase the chance of getting dangerous side effects.**
- **Do not take other medicines without your doctor's approval.** Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you sleepy.

What are the Possible Side Effects of Oxycodone Hydrochloride Extended-Release Tablets?

Call your doctor or get medical help right away if

- your breathing slows down
- you feel faint, dizzy, confused, or have any other unusual symptoms

Some of the common side effects of Oxycodone Hydrochloride Extended-Release Tablets are nausea, vomiting, dizziness, drowsiness, constipation, itching, dry mouth, sweating, weakness, and headache. Some of these side effects may decrease with continued use.

There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while using Oxycodone Hydrochloride Extended-Release Tablets. We do not know how often patients with continuing (chronic) pain become addicted to narcotics, but the risk has been reported to be small.

These are not all the possible side effects of Oxycodone Hydrochloride Extended-Release Tablets. For a complete list, ask your doctor or pharmacist.

General Advice About Oxycodone Hydrochloride Extended-Release Tablets

- Do not use Oxycodone Hydrochloride Extended-Release Tablets for conditions for which it was not prescribed.
- Do not give Oxycodone Hydrochloride Extended-Release Tablets to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems, including death.

This leaflet summarizes the most important information about Oxycodone Hydrochloride Extended-Release Tablets. If you would like more information, talk with your doctor. Also,

you can ask your pharmacist or doctor for information about Oxycodone Hydrochloride Extended-Release Tablets that is written for health professionals.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

412542/February, 2003

Final_*revision1*
February 19, 2004

ENDO GENERIC PRODUCTS

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS
80 mg

CII

R_x only

80 mg FOR USE IN OPIOID- TOLERANT PATIENTS ONLY

WARNING:

Oxycodone hydrochloride extended-release tablets are an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

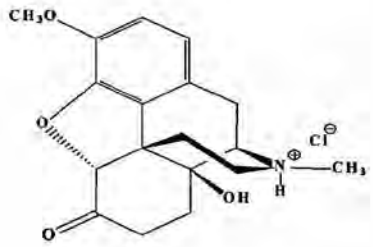
Oxycodone hydrochloride extended-release tablets are NOT intended for use as a prn analgesic.

Oxycodone hydrochloride extended-release 80 mg tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

Oxycodone hydrochloride extended-release tablets ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

Oxycodone hydrochloride extended-release tablets are an opioid analgesic supplied in 80 mg tablet strength for oral administration. The tablet strength describes the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.82

The chemical formula is 4, 5-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio methacrylate copolymer, colloidal silicon dioxide, D&C Yellow #10, FD&C Blue #2, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium hydroxide, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, stearic acid, and titanium dioxide.

CLINICAL PHARMACOLOGY

Central Nervous System

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic affect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone hydrochloride extended-release tablet overdose (see **OVERDOSAGE**).

Gastrointestinal Tract and Other Smooth Muscle
Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System
Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration – Efficacy Relationships
Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall "drug effect," analgesia and feelings of "relaxation."

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients need to be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration – Adverse Experience Relationships
Oxycodone hydrochloride extended-release tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see **DOSAGE AND ADMINISTRATION**), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

PHARMACOKINETICS AND METABOLISM

The activity of oxycodone hydrochloride extended-release tablets is primarily due to the parent drug oxycodone. Oxycodone hydrochloride extended-release tablets are designed to provide controlled delivery of oxycodone over 12 hours.

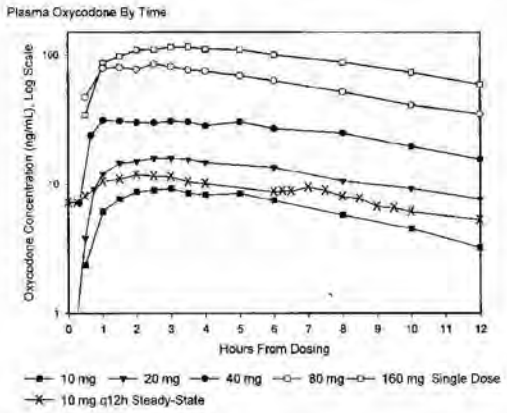
Breaking, chewing or crushing oxycodone hydrochloride extended-release tablets eliminates the controlled delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from oxycodone hydrochloride extended-release tablets is pH independent. Oxycodone is well absorbed from oxycodone hydrochloride extended-release tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of oxycodone hydrochloride extended-release tablets to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Dose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of oxycodone hydrochloride extended-release tablets was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers, the t½ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, oxycodone hydrochloride extended-release tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Another study established that the 160 mg tablet is bioequivalent to 2 x 80 mg tablets as well as to 4 x 40 mg for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 2 below). Given the short half-life of elimination of oxycodone from oxycodone hydrochloride extended-release tablets, steady-state plasma concentrations of oxycodone



are achieved within 24-36 hours of initiation of dosing with oxycodone hydrochloride extended-release tablets. In a study comparing 10 mg of oxycodone hydrochloride extended-release tablets every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the oxycodone hydrochloride extended-release tablets than for the immediate-release formulation.

Table 1
Mean [% coefficient variation]

Regimen	Dosage Form	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg oxycodone hydrochloride extended-release tablets	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg oxycodone hydrochloride extended-release tablets	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg oxycodone hydrochloride extended-release tablets	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg oxycodone hydrochloride extended-release tablets*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a
Multiple Dose	10 mg oxycodone hydrochloride extended-release tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

Table 2
Mean [% coefficient variation]

Regimen	Dosage Form	AUC_{∞} (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	4 x 40 mg oxycodone hydrochloride extended-release tablets*	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
	2 x 80 mg oxycodone hydrochloride extended-release tablets*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
	1 x 160 mg oxycodone hydrochloride extended-release tablets*	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

† for single-dose AUC = $AUC_{0\text{-}inf}$; for multiple dose AUC = $AUC_{0\text{-}\tau}$
* data obtained while volunteers received naltrexone which can enhance absorption.

Oxycodone hydrochloride extended-release tablets ARE NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that oxycodone hydrochloride extended-release tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects
Food has no significant effect on the extent of absorption of oxycodone from oxycodone hydrochloride extended-release tablets. However, the peak plasma concentration of oxycodone increased by 25% when oxycodone hydrochloride extended-release 160 mg tablet was administered with a high fat meal.

Distribution
Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen and brain. Oxycodone has been found in breast milk (see **PRECAUTIONS**).

Metabolism
Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see **Drug-Drug Interactions**).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone {PRIVATE "TYPE=PICT;ALT=Less than or equal to"}≤14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in t½ of elimination for oxycodone of only 1 hour (see **PRECAUTIONS**).

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The t½ elimination for oxycodone increased by 2.3 hours (see **PRECAUTIONS**).

Drug-Drug Interactions (see **PRECAUTIONS**)

Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic anti-depressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.

Pharmacodynamics

A single-dose, double-blind, placebo- and dose-controlled study was conducted using oxycodone hydrochloride extended-release tablets (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. Twenty and 30 mg of oxycodone hydrochloride extended-release tablets were superior in reducing pain compared with placebo, and this difference was statistically significant. The onset of analgesic action with oxycodone hydrochloride extended-release tablets occurred within 1 hour in most patients following oral administration.

CLINICAL TRIALS

A double-blind placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with chronic, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, 20 mg oxycodone hydrochloride extended-release tablets q12h but not 10 mg oxycodone hydrochloride extended-release tablets q12h decreased pain compared with placebo, and this difference was statistically significant.

INDICATIONS AND USAGE

Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone

hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Oxycodone hydrochloride extended-release tablets are **NOT** intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the immediate post-operative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persists for an extended period of time. Oxycodone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

Oxycodone hydrochloride extended-release tablets are contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone hydrochloride extended-release tablets are contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Oxycodone hydrochloride extended-release 80 mg tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids

Oxycodone hydrochloride extended-release 80 mg tablets are for use in opioid tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet. Care should be taken in the prescribing of this tablet strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Oxycodone hydrochloride extended-release tablets have been reported as being abused by crushing, chewing,

snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

Oxycodone hydrochloride extended-release tablets are a mu-agonist opioid with an abuse liability similar to morphine and are a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Oxycodone hydrochloride extended-release tablets, like other opioids, have been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Oxycodone hydrochloride extended-release tablets consist of a polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression
Respiratory depression is the chief hazard from oxycodone, the active ingredient in oxycodone hydrochloride extended-release tablets, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury
Oxycodone hydrochloride extended-release tablets may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Hypotensive Effect
Oxycodone hydrochloride extended-release tablets may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS
General
Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of oxycodone hydrochloride extended-release tablets is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with Other CNS Depressants
Oxycodone hydrochloride extended-release tablets should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of oxycodone hydrochloride extended-release tablets.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics
Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Post-Operative Use

Oxycodone hydrochloride extended-release tablets are not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

Oxycodone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).

Patients who are already receiving oxycodone hydrochloride extended-release tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

Oxycodone hydrochloride extended-release tablets and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease
Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence
Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers
If clinically advisable, patients receiving oxycodone hydrochloride extended-release tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that oxycodone hydrochloride extended-release tablets contain oxycodone, which is a morphine-like substance.

2. Patients should be advised that oxycodone hydrochloride extended-release tablets were designed to work properly only if swallowed whole. Oxycodone hydrochloride extended-release tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of oxycodone hydrochloride extended-release tablets without consulting the prescribing professional.
5. Patients should be advised that oxycodone hydrochloride extended-release tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine oxycodone hydrochloride extended-release tablets with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that oxycodone hydrochloride extended-release tablets are a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that if they have been receiving treatment with oxycodone hydrochloride extended-release tablets for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the oxycodone hydrochloride extended-release tablets dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
10. Patients should be instructed to keep oxycodone hydrochloride extended-release tablets in a secure place out of the reach of children. When oxycodone hydrochloride extended-release tablets are no longer needed, the unused tablets should be destroyed by flushing down the toilet.

See text of Patient Package Insert, which appears after the **HOW SUPPLIED** section.

Use in Drug and Alcohol Addiction

Oxycodone hydrochloride extended-release tablets are an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including oxycodone hydrochloride extended-release tablets, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

Oxycodone hydrochloride extended-release tablets, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 mcg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 mcg/mL and with activation 48 hours after exposure at doses of up to 5000 mcg/mL, and in the *in vivo* bone marrow micronucleus test in mice (at plasma levels of up to 48 mcg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 mcg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 mcg/mL or greater with metabolic activation and at 400 mcg/mL or greater without metabolic activation.

Pregnancy

Teratogenic Effects—Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Oxycodone hydrochloride extended-release tablets are not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving oxycodone hydrochloride extended-release tablets because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of oxycodone hydrochloride extended-release tablets have not been established in pediatric patients below the age of 18. **It must be remembered that oxycodone hydrochloride extended-release tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see **Pharmacokinetics and Metabolism**). Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride extended-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received oxycodone hydrochloride extended-release tablets. Thus, the usual doses and dosing intervals are appropriate for these patients.

As with all opioids, the starting dose should be reduced to 1/3 to ½ of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of oxycodone hydrochloride extended-release tablets in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

The safety of oxycodone hydrochloride extended-release tablets was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received oxycodone hydrochloride extended-release tablets in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with oxycodone hydrochloride extended-release tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with oxycodone hydrochloride extended-release tablets are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as oxycodone hydrochloride extended-release tablet therapy is continued and some degree of tolerance is developed.

Clinical trials comparing oxycodone hydrochloride extended-release tablets with immediate-release oxycodone and placebo revealed a similar adverse event profile between oxycodone hydrochloride extended-release tablets and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

Table 3

	Oxycodone Hydrochloride Extended-Release Tablets (n=227) (%)	Immediate-Release (n=225) (%)	Placebo (n=45) (%)
Constipation	23	26	7
Nausea	23	27	11
Somnolence	23	24	4
Dizziness	13	16	9
Pruritus	13	12	2
Vomiting	12	14	7
Headache	7	8	7
Dry Mouth	6	7	2
Asthenia	6	7	--
Sweating	5	6	2

The following adverse experiences were reported in oxycodone hydrochloride extended-release tablet treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in post marketing experience:

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

Urogenital: amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of oxycodone hydrochloride extended-release tablets, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when oxycodone hydrochloride extended-release tablets are abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including oxycodone hydrochloride extended-release tablets, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE.

OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

One oxycodone hydrochloride extended-release 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets (see DOSAGE AND ADMINISTRATION).

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain requiring treatment with a strong opioid for

continuous, around-the-clock analgesia for an extended period of time. The extended-release nature of the formulation allows oxycodone hydrochloride extended-release tablets to be effectively administered every 12 hours (see **CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM.**) While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Health care professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring [See **BOXED WARNINGS**].

Initiation of Therapy
It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

(1) the general condition and medical status of the patient;

(2) the daily dose, potency, and kind of the analgesic(s) the patient has been taking;

(3) the reliability of the conversion estimate used to calculate the dose of oxycodone;

(4) the patient's opioid exposure and opioid tolerance (if any);

(5) special safety issues associated with conversion to oxycodone hydrochloride extended-release tablet doses at or exceeding 160 mg q12h (see **Special instructions for oxycodone hydrochloride extended-release 80 mg and 160 mg tablets**); and

(6) the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of oxycodone hydrochloride extended-release tablets in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see **PRECAUTIONS: Drug-Drug Interactions**).

For initiation of oxycodone hydrochloride extended-release tablet therapy for patients previously taking opioids, the conversion ratios from Foley, KM. [NEJM, 1985; 313:84-95], found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

Experience indicates a reasonable starting dose of oxycodone hydrochloride extended-release tablets for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg q12h. If a non-opioid analgesic is being provided, it may be continued. Oxycodone hydrochloride extended-release tablets should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. When converting from oxycodone, divide the 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of oxycodone hydrochloride extended-release tablets.
3. Round down to a dose which is appropriate for the tablet strengths available (10 mg, 20 mg, 40 mg, and 80 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when oxycodone hydrochloride extended-release tablet therapy is initiated.

5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

Table 4

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*
(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	--
Codeine	0.15	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

***To be used only for conversion to oral oxycodone.** For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of a suitable short-acting analgesic.

Oxycodone hydrochloride extended-release tablets can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see **PRECAUTIONS**).

Conversion from Transdermal Fentanyl to Oxycodone Hydrochloride Extended-Release Tablets
Eighteen hours following the removal of the transdermal fentanyl patch, oxycodone hydrochloride extended-release tablet treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of oxycodone hydrochloride extended-release tablets, should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences
Most patients receiving opioids, especially those who are opioid- naive, will experience side effects. Frequently the side effects from oxycodone hydrochloride extended-release tablets are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Individualization of Dosage
Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from

10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the health-care team, the patient and the caregiver/family.

Special Instructions for Oxycodone Hydrochloride Extended-Release 80 mg Tablets
(For use in opioid-tolerant patients only)

Oxycodone hydrochloride extended-release 80 mg tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet. Care should be taken in the prescribing of this tablet strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

One oxycodone hydrochloride extended-release 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets.

Supplemental Analgesia
Most patients given around-the-clock therapy with controlled-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Maintenance of Therapy
The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy
When the patient no longer requires therapy with oxycodone hydrochloride extended-release tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from Oxycodone Hydrochloride Extended-Release Tablets to Parenteral Opioids
To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING
Oxycodone hydrochloride extended-release tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

Oxycodone hydrochloride extended-release tablets have been targeted for theft and diversion by criminals.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED
Oxycodone hydrochloride extended-release tablets are supplied as follows:

80 mg
Unscored, coated, round, green tablet, imprinted with "E710" on one side and "80" on the other.

Bottles of 30 with a child-resistant closure NDC 60951-710-30

Bottles of 500 NDC 60951-710-85

Desiccant enclosed in all bottles.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container, as defined in the USP, with a child-resistant closure (as required).

CAUTION
DEA Order Form Required.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317

Printed in U.S.A.

6548-81/May, 2002

PATIENT INFORMATION

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS CII

Oxycodone Hydrochloride Extended-Release Tablets, 80 mg

Rx only

Read this information carefully before you take Oxycodone Hydrochloride Extended-Release Tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if Oxycodone Hydrochloride Extended-Release Tablets are right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information I Should Know About Oxycodone Hydrochloride Extended-Release Tablets?

- **Use Oxycodone Hydrochloride Extended-Release Tablets the way your doctor tells you to.**
- **Use Oxycodone Hydrochloride Extended-Release Tablets only for the condition for which it was prescribed.**

Final_*revision1*
February 19, 2004

- **Oxycodone Hydrochloride Extended-Release Tablets are not for occasional ("as needed") use.**
- **Swallow the tablets whole.** Do not break, crush, dissolve, or chew them before swallowing. Oxycodone Hydrochloride Extended-Release Tablets work properly over 12 hours only when swallowed whole. **If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.**
- **Keep Oxycodone Hydrochloride Extended-Release Tablets out of the reach of children.** Accidental overdose by a child is dangerous and may result in death.
- **Prevent theft and misuse.** Oxycodone Hydrochloride Extended-Release Tablets contain a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What are Oxycodone Hydrochloride Extended-Release Tablets?

Oxycodone Hydrochloride Extended-Release Tablets are tablets that come in several strengths and contain the medicine oxycodone (ox-e-KOE-done). This medicine is a painkiller like morphine. Oxycodone Hydrochloride Extended-Release Tablets treat moderate to severe pain that is expected to last for an extended period of time. Use Oxycodone Hydrochloride Extended-Release Tablets regularly during treatment. They contain enough medicine to last for up to twelve hours.

Who Should Not Take Oxycodone Hydrochloride Extended-Release Tablets?

Do not take Oxycodone Hydrochloride Extended-Release Tablets if

- your doctor did not prescribe Oxycodone Hydrochloride Extended-Release Tablets for you.
- your pain is mild or will go away in a few days.
- your pain can be controlled by occasional use of other painkillers.
- you have severe asthma or severe lung problems.
- you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox, Tylenol with Codeine, or Vicodin). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
- you had surgery less than 12 – 24 hours ago and you were not taking Oxycodone Hydrochloride Extended-Release Tablets just before surgery.

Your doctor should know about all your medical conditions before deciding if Oxycodone Hydrochloride Extended-Release Tablets are right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures

- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking Oxycodone Hydrochloride Extended-Release Tablets.

If you are pregnant or plan to become pregnant, talk with your doctor. Oxycodone Hydrochloride Extended-Release Tablets may not be right for you. **Tell your doctor if you are breast feeding.** Oxycodone Hydrochloride Extended-Release Tablets will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with Oxycodone Hydrochloride Extended-Release Tablets, especially if they cause drowsiness.

How Should I Take Oxycodone Hydrochloride Extended-Release Tablets?

- **Follow your doctor's directions exactly.** Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take Oxycodone Hydrochloride Extended-Release Tablets more often than prescribed.
- **Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.**
- **If you miss a dose,** take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.
- **In case of overdose,** call your local emergency number or poison control center right away.
- **Review your pain regularly with your doctor** to determine if you still need Oxycodone Hydrochloride Extended-Release Tablets.

If you continue to have pain or bothersome side effects, call your doctor.

Stopping Oxycodone Hydrochloride Extended-Release Tablets. Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking Oxycodone Hydrochloride Extended-Release Tablets all at once if you have been taking it for more than a few days.

After you stop taking Oxycodone Hydrochloride Extended-Release Tablets, flush the unused tablets down the toilet.

What Should I Avoid While Taking Oxycodone Hydrochloride Extended-Release Tablets?

- **Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities** until you know how you react to this medicine. Oxycodone Hydrochloride Extended-Release Tablets can make you sleepy.

- **Do not drink alcohol while using Oxycodone Hydrochloride Extended-Release Tablets. It may increase the chance of getting dangerous side effects.**
- **Do not take other medicines without your doctor's approval.** Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you sleepy.

What are the Possible Side Effects of Oxycodone Hydrochloride Extended-Release Tablets?

Call your doctor or get medical help right away if

- your breathing slows down
- you feel faint, dizzy, confused, or have any other unusual symptoms

Some of the common side effects of Oxycodone Hydrochloride Extended-Release Tablets are nausea, vomiting, dizziness, drowsiness, constipation, itching, dry mouth, sweating, weakness, and headache. Some of these side effects may decrease with continued use.

There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while using Oxycodone Hydrochloride Extended-Release Tablets. We do not know how often patients with continuing (chronic) pain become addicted to narcotics, but the risk has been reported to be small.

These are not all the possible side effects of Oxycodone Hydrochloride Extended-Release Tablets. For a complete list, ask your doctor or pharmacist.

General Advice About Oxycodone Hydrochloride Extended-Release Tablets

- Do not use Oxycodone Hydrochloride Extended-Release Tablets for conditions for which it was not prescribed.
- Do not give Oxycodone Hydrochloride Extended-Release Tablets to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems, including death.

This leaflet summarizes the most important information about Oxycodone Hydrochloride Extended-Release Tablets. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about Oxycodone Hydrochloride Extended-Release Tablets that is written for health professionals.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

6548-81/May, 2002

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February 19, 2004

APPENDIX 2 – OXYCODONE ER GENERIC PATIENT PACKAGE INSERT

PATIENT INFORMATION

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS

Oxycodone Hydrochloride Extended-Release Tablets, 10 mg
Oxycodone Hydrochloride Extended-Release Tablets, 20 mg
Oxycodone Hydrochloride Extended-Release Tablets, 40 mg

Read this information carefully before you take Oxycodone Hydrochloride Extended-Release Tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if Oxycodone Hydrochloride Extended-Release Tablets are right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information I Should Know About Oxycodone Hydrochloride Extended-Release Tablets?

- **Use Oxycodone Hydrochloride Extended-Release Tablets the way your doctor tells you to.**
- **Use Oxycodone Hydrochloride Extended-Release Tablets only for the condition for which it was prescribed.**
- **Oxycodone Hydrochloride Extended-Release Tablets are not for occasional ("as needed") use.**
- **Swallow the tablets whole.** Do not break, crush, dissolve, or chew them before swallowing. Oxycodone Hydrochloride Extended-Release Tablets work properly over 12 hours only when swallowed whole. **If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.**
- **Keep Oxycodone Hydrochloride Extended-Release Tablets out of the reach of children.** Accidental overdose by a child is dangerous and may result in death.
- **Prevent theft and misuse.** Oxycodone Hydrochloride Extended-Release Tablets contain a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What are Oxycodone Hydrochloride Extended-Release Tablets?

Oxycodone Hydrochloride Extended-Release Tablets are tablets that come in several strengths and contain the medicine oxycodone (ox-e-KOE-done). This medicine is a painkiller like morphine. Oxycodone Hydrochloride Extended-Release Tablets treat moderate to severe pain that is expected to last for an extended period of time. Use Oxycodone Hydrochloride Extended-Release Tablets regularly during treatment. They contain enough medicine to last for up to twelve hours.

Who Should Not Take Oxycodone Hydrochloride Extended-Release Tablets?

Do not take Oxycodone Hydrochloride Extended-Release Tablets if

- your doctor did not prescribe Oxycodone Hydrochloride Extended-Release Tablets for you.
- your pain is mild or will go away in a few days.
- your pain can be controlled by occasional use of other painkillers.
- you have severe asthma or severe lung problems.
- you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox, Tylenol with Codeine, or Vicodin). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
- you had surgery less than 12 – 24 hours ago and you were not taking Oxycodone Hydrochloride Extended-Release Tablets just before surgery.

Your doctor should know about all your medical conditions before deciding if Oxycodone Hydrochloride Extended-Release Tablets are right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell

your doctor before taking Oxycodone Hydrochloride Extended-Release Tablets.

If you are pregnant or plan to become pregnant, talk with your doctor. Oxycodone Hydrochloride Extended-Release Tablets may not be right for you. **Tell your doctor if you are breast feeding.** Oxycodone Hydrochloride Extended-Release Tablets will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with Oxycodone Hydrochloride Extended-Release Tablets, especially if they cause drowsiness.

How Should I Take Oxycodone Hydrochloride Extended-Release Tablets?

- **Follow your doctor's directions exactly.** Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take Oxycodone Hydrochloride Extended-Release Tablets more often than prescribed.
- **Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.**
- **If you miss a dose,** take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.
- **In case of overdose,** call your local emergency number or poison control center right away.
- **Review your pain regularly with your doctor** to determine if you still need Oxycodone Hydrochloride Extended-Release Tablets.

If you continue to have pain or bothersome side effects, call your doctor.

Stopping Oxycodone Hydrochloride Extended-Release Tablets. Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking Oxycodone Hydrochloride Extended-Release Tablets all at once if you have been taking it for more than a few days.

After you stop taking Oxycodone Hydrochloride Extended-Release Tablets, flush the unused tablets down the toilet.

What Should I Avoid While Taking Oxycodone Hydrochloride Extended-Release Tablets?

- **Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities** until you know how you react to this medicine. Oxycodone Hydrochloride Extended-Release Tablets can make you sleepy.
- **Do not drink alcohol while using Oxycodone Hydrochloride Extended-Release Tablets. It may increase the chance of getting dangerous side effects.**
- **Do not take other medicines without your doctor's approval.** Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you sleepy.

What are the Possible Side Effects of Oxycodone Hydrochloride Extended-Release Tablets?

Call your doctor or get medical help right away if

- your breathing slows down
- you feel faint, dizzy, confused, or have any other unusual symptoms

Some of the common side effects of Oxycodone Hydrochloride Extended-Release Tablets are nausea, vomiting, dizziness, drowsiness, constipation, itching, dry mouth, sweating, weakness, and headache. Some of these side effects may decrease with continued use.

There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while using Oxycodone Hydrochloride Extended-Release Tablets. We do not know how often patients with continuing (chronic) pain become addicted to narcotics, but the risk has been reported to be small.

These are not all the possible side effects of Oxycodone Hydrochloride Extended-Release Tablets. For a complete list, ask your doctor or pharmacist.

General Advice About Oxycodone Hydrochloride Extended-Release Tablets

- Do not use Oxycodone Hydrochloride Extended-Release Tablets for conditions for which it was not prescribed.
- Do not give Oxycodone Hydrochloride Extended-Release Tablets to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems, including death.

This leaflet summarizes the most important information about Oxycodone Hydrochloride Extended-Release Tablets. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about Oxycodone Hydrochloride Extended-Release Tablets that is written for health professionals.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

412642/February, 2003

Final_*revision1*
February 19, 2004

PATIENT INFORMATION

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS CII

Oxycodone Hydrochloride Extended-Release Tablets, 80 mg

Rx only

Read this information carefully before you take Oxycodone Hydrochloride Extended-Release Tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if Oxycodone Hydrochloride Extended-Release Tablets are right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information I Should Know About Oxycodone Hydrochloride Extended-Release Tablets?

- **Use Oxycodone Hydrochloride Extended-Release Tablets the way your doctor tells you to.**
- **Use Oxycodone Hydrochloride Extended-Release Tablets only for the condition for which it was prescribed.**
- **Oxycodone Hydrochloride Extended-Release Tablets are not for occasional ("as needed") use.**
- **Swallow the tablets whole.** Do not break, crush, dissolve, or chew them before swallowing. Oxycodone Hydrochloride Extended-Release Tablets work properly over 12 hours only when swallowed whole. **If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.**
- **Keep Oxycodone Hydrochloride Extended-Release Tablets out of the reach of children.** Accidental overdose by a child is dangerous and may result in death.
- **Prevent theft and misuse.** Oxycodone Hydrochloride Extended-Release Tablets contain a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What are Oxycodone Hydrochloride Extended-Release Tablets?

Oxycodone Hydrochloride Extended-Release Tablets are tablets that come in several strengths and contain the medicine oxycodone (ox-e-KOE-done). This medicine is a painkiller like morphine. Oxycodone Hydrochloride Extended-Release Tablets treat moderate to severe pain that is expected to last for an extended period of time. Use Oxycodone Hydrochloride Extended-Release Tablets regularly during treatment. They contain enough medicine to last for up to twelve hours.

Who Should Not Take Oxycodone Hydrochloride Extended-Release Tablets?

Do not take Oxycodone Hydrochloride Extended-Release Tablets if

- your doctor did not prescribe Oxycodone Hydrochloride Extended-Release Tablets for you.
- your pain is mild or will go away in a few days.
- your pain can be controlled by occasional use of other painkillers.
- you have severe asthma or severe lung problems.
- you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox, Tylenol with Codeine, or Vicodin). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
- you had surgery less than 12 – 24 hours ago and you were not taking Oxycodone Hydrochloride Extended-Release Tablets just before surgery.

Your doctor should know about all your medical conditions before deciding if Oxycodone Hydrochloride Extended-Release Tablets are right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking Oxycodone Hydrochloride Extended-Release Tablets.

If you are pregnant or plan to become pregnant, talk with your doctor. Oxycodone Hydrochloride Extended-Release Tablets may not be right for you. **Tell your doctor if you are breast feeding.** Oxycodone Hydrochloride Extended-Release Tablets will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with Oxycodone Hydrochloride Extended-Release Tablets, especially if they cause drowsiness.

How Should I Take Oxycodone Hydrochloride Extended-Release Tablets?

- **Follow your doctor's directions exactly.** Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take Oxycodone Hydrochloride Extended-Release Tablets more often than prescribed.
- **Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.**

- **If you miss a dose,** take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.
- **In case of overdose,** call your local emergency number or poison control center right away.
- **Review your pain regularly with your doctor** to determine if you still need Oxycodone Hydrochloride Extended-Release Tablets.
- **You may see tablets in your stools (bowel movements).** Do not be concerned. Your body has already absorbed the medicine.

If you continue to have pain or bothersome side effects, call your doctor.

Stopping Oxycodone Hydrochloride Extended-Release Tablets. Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking Oxycodone Hydrochloride Extended-Release Tablets all at once if you have been taking it for more than a few days.

After you stop taking Oxycodone Hydrochloride Extended-Release Tablets, flush the unused tablets down the toilet.

What Should I Avoid While Taking Oxycodone Hydrochloride Extended-Release Tablets?

- **Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities** until you know how you react to this medicine. Oxycodone Hydrochloride Extended-Release Tablets can make you sleepy.

- **Do not drink alcohol while using Oxycodone Hydrochloride Extended-Release Tablets. It may increase the chance of getting dangerous side effects.**

- **Do not take other medicines without your doctor's approval.** Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you sleepy.

What are the Possible Side Effects of Oxycodone Hydrochloride Extended-Release Tablets?

Call your doctor or get medical help right away if
- your breathing slows down
- you feel faint, dizzy, confused, or have any other unusual symptoms

Some of the common side effects of Oxycodone Hydrochloride Extended-Release Tablets are nausea, vomiting, dizziness, drowsiness, constipation, itching, dry mouth, sweating, weakness, and headache. Some of these side effects may decrease with continued use.

There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while using Oxycodone Hydrochloride Extended-Release Tablets. We do not know how often patients with continuing (chronic) pain become addicted to narcotics, but the risk has been reported to be small.

These are not all the possible side effects of Oxycodone Hydrochloride Extended-Release Tablets. For a complete list, ask your doctor or pharmacist.

General Advice About Oxycodone Hydrochloride Extended-Release Tablets

- Do not use Oxycodone Hydrochloride Extended-Release Tablets for conditions for which it was not prescribed.
- Do not give Oxycodone Hydrochloride Extended-Release Tablets to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems, including death.

This leaflet summarizes the most important information about Oxycodone Hydrochloride Extended-Release Tablets. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about Oxycodone Hydrochloride Extended-Release Tablets that is written for health professionals.

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

6560-00/May, 2002

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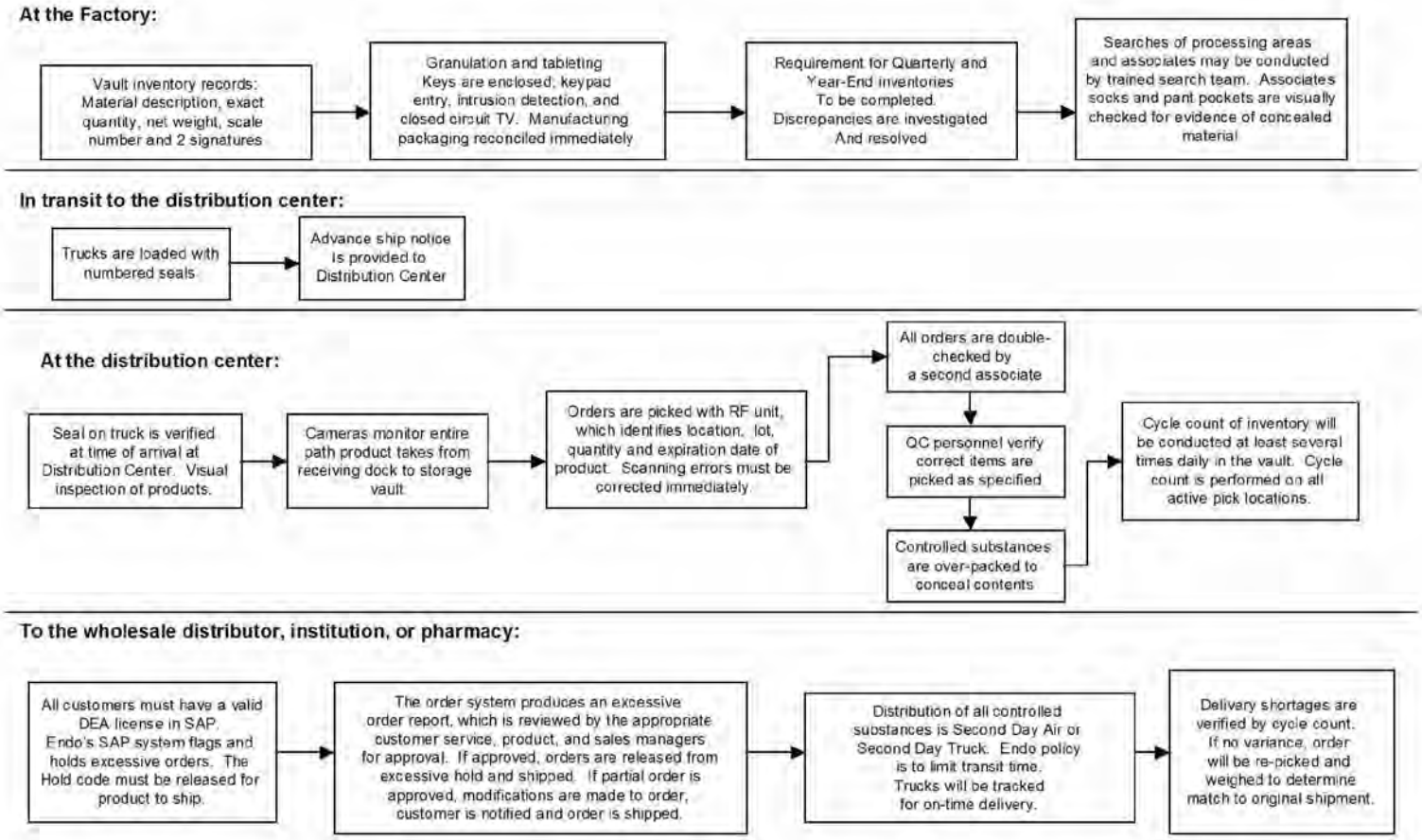
February 19, 2004

APPENDIX 3 –MANUFACTURING AND DISTRIBUTION CHAIN CONTROLS

Figure 1. Endo Safeguards to Prevent Opioid Diversion



APPENDIX 4 – ORDER PROCESSING AND DISTRIBUTION

Excessive Orders Management

ENDO Pharmaceuticals SAP Order Management System flags and holds all excessive orders for all Endo products (controlled substances II, III and ambient products). The order remains on hold and does not ship until the hold code on the order is released.

Specifically, orders are put on excessive hold when:

- The order exceeds the past 3 months average shipped quantity by 15%, and/or
- The order exceeds the past 12 months average shipped quantity by 15%.

The system produces a report that provides customer information to Customer Service. Customer Service Representatives are responsible for calling customers on all excessive orders to inquire about the increase in the ordering. All of this information is recorded in the customer order notes within SAP.

This information is then passed along to the Manager, Customer Service and Distribution. The Manager, Customer Service and Distribution then forwards this data along with the Excessive Report to the appropriate Product Managers and Director of Sales for approval. If approved by those individuals, those orders are then released from Excessive hold and shipped. If partial quantities are approved, Customer Service modifies the order, notifies the customer and then the order is shipped. If the entire order is rejected, Customer Service also notifies the customer.

Receipt Process

All inbound product shipments are received into Quarantine Hold.

Endo Pharmaceuticals will notify the warehouse with an advance shipment notification for all shipments prior to arrival. Information will include product code, lot number, quantity, Manufacturer, and Purchase order number.

Upon arrival of the truck in Memphis, receivers will verify that all seals are intact and match the freight bill prior to opening the doors.

The receiving associates will visually inspect all inbound products before and during the off loading process. If any discrepancies are found (i.e., damages, shortages, overages) the receiving associate will contact the operations supervisor and the QA representative on site.

All inbound CII product will be off loaded to the secured vault area immediately upon arrival. Cameras will monitor the path the product follows from the receiving dock to the storage vault.

Product will be physically counted. Once the count is complete the product will be physically bagged with an orange quarantine bag and a quarantine placard will be applied to each pallet.

The actual quantities, lot number and expiration dates are posted via the RF function.

Picking Process

All CII orders are picked with a RF unit. This RF unit will identify the location, lot, quantity and expiration date of the product that needs to be picked. Each bar code is scanned with the RF to identify the product that needs to be picked. If the wrong product is scanned an error or a warning message will appear on the RF unit. The error must be corrected before moving on to the next line of the order.

Any discrepancies (location, product, lot expiration or quantity) are bought to the supervisor's attention immediately for resolution.

All orders are double checked by another warehouse associate. The orders are checked for product, lot, and quantity.

Upon completion of the pick and the double check process, QC personnel will verify that the correct items have been picked for the order as specified on the pick/pack document.

If a discrepancy is found the QC checker will immediately bring it to the attention of the Operations Supervisor and QA Supervisor.

Once it has been confirmed that the product picked matches the orders, the QC checker will check the release list and client hold list to verify the lot number picked is in "released status" and thus available for distribution.

The QC checker will stay with the order until the order has been packed for shipping.

The packing list for each order will include instructions to notify Customer Service within 48 hours for any discrepancies.

Product Packing

All controlled substances are enclosed in a secondary corrugate container before they are shipped. Specifically, there is no way to know what is in the primary container, because it is over packed to secure it. Full pallets of controlled substance are enclosed with a corrugate pallet cover and then the entire pallet is wrapped with black wrap.

Distribution

Distribution of all of Endo's controlled substances and ambient products will be by second day air and/or 2nd day truck. Endo will continue its policy to limit the amount of time that all products, especially the controlled substances, are in transit.

Customer Service will proactively track all EN3218 shipments throughout each day to ensure that the product was delivered on time for the first three months after launch. If any EN3218 shipment is not delivered per the delivery schedule, the order will be tracked down immediately by customer service.

Cycle count of inventory is conducted daily in the vault prior to any orders shipping. A cycle count is performed on ALL active picking locations after a batch of orders (each batch is approximately 40-50 orders).

After a batch of orders is completed, a warehouse associate will generate a report that indicates all locations that need to be counted. A warehouse associate will go to each location and count the number of units in the location. After the count is completed the count sheet is provided to the team lead or supervisor. The team lead or supervisor will run another report that will indicate the number of units that should be in each location. If the count does not match, the supervisor will count the locations again. If the count still does not match, the warehouse will begin opening all the packages until they can find the mistake.

No orders are shipped until the inventory is reconciled.

Reported Shortages

Currently, customers call Customer Service with complaints regarding shortages. Customer Service tracks, via an Error Log, all Customer Service errors (shortages, damages, mis-shipments etc). If the error is a short ship, that is less is received then shipped, Customer Service and Distribution immediately begin to analyze the situation to determine cause and path forward.

A shortage reported by a customer will be verified in the following manner:

(1) An inventory cycle count will be conducted on the product in question to determine whether a variance exists; that is, does physical inventory match system inventory.
(2) If no variance is found, the order will be re-picked and re-weighed to check if the weight supports the original weight of the shipments

APPENDIX 5 – ENDO ESRB STANDARD OPERATING PROCEDURE

Endo Pharmaceuticals Inc.

ENDO SAFETY REVIEW BOARD (ESRB)	Effective Date: 01/30/02	Doc. No.: ENDO-1825-01
	Supersedes: NEW	Page: 1 of 5
	Document Type: STANDARD OPERATING PROCEDURE	
	Documentation Signature:	

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REFERENCE COPY

1.0 PURPOSE

- To establish a multidisciplinary board that is responsible for reviewing all adverse event (AE) data reported from clinical research (Phase I thru IV) for both Investigational and marketed drugs and spontaneous reports for marketed drugs.
- To assure public safety through timely review and incorporation of safety information into prescribing information for clinicians.
- To assure adherence to FDA regulatory requirements, Good Clinical Practices (GCP) guidelines and to the policies of Endo Pharmaceuticals, Inc. with respect to receiving, tracking, documenting, and reporting of adverse events.
- To determine a global course of action for each product based on safety data received over time.
- Miscellaneous (Safety Related Crises)
  1. Prepare action plan in the event of an AE related crisis (e.g., multiple spontaneous reports of hepatic or cardiac toxicities)
  2. Provide medical/safety information and investigation follow-up to the Endo Crisis Management Team.

1.1 Responsibilities Of Endo Safety Review Board (ESRB)

The board will be charged with ensuring that proper follow-up has occurred and jointly agree on the following action items (whichever is appropriate on a case by case basis) for each product reviewed:

Investigational Drugs (Phase I, II, III, & IIIB)

1. Review Investigator Brochure (IB) safety section for consistency and completeness with the knowledge regarding the product at the time of IB creation
2. Recommend amendments to Investigators Brochure to include new safety information
3. Recommend initiation of a studies to further investigate & characterize the safety of the investigational drug.
4. Review the Integrated Safety Summary for New Drug Application (NDA) submissions
5. Review annual Investigational New Drug (IND) safety reports
6. No action necessary

1.1 Responsibilities Of Endo Safety Review Board (ESRB) (Cont'd)

Marketed Drugs (Phase IV, Registries) & Spontaneous Reports (consumer & healthcare professional)

1. Recommend Amendments to the Package Insert to include new safety information
2. Recommend initiation of a studies to further investigate & characterize the safety of the marketed drug.
3. Review Periodic Safety Reports for marketed products for any new trends that may require further action
4. No action necessary

2.0 GENERAL INFORMATION

2.1 Responsibility

It is the responsibility of the Endo Safety Review Board (ESRB) members to ensure compliance with this Standard Operating Procedure.

2.2 References

- FDA Regulations – 21 CFR 310, 312, 314 and 600, April 2001
- FDA Guideline For Post-marketing Reporting of Adverse Drug Experiences, March 1992
- Guideline for GCP, Federal Register May 9, 1997
- SOP DOC. No. ENDO-1329 Endo Employee Adverse Event Reporting
- SOP Doc. No. ENDO-1328 Medical Affairs Standard Procedure for the Receipt, Tracking, and Reporting of Adverse Events related to Marketed Drugs.

3.0 DEFINITIONS

Investigational Drug: Any drug that has yet to be approved by the FDA and is being studied under an IND for possible approval in the future.

Marketed Drug: Any drug with an approved NDA, Abbreviated New Drug Application (ANDA) or with a DESI drug designation.

Endo Safety Review Board (ESRB):

The ESRB will consist of a core team from the following disciplines and will meet quarterly and on an "as needed" basis to deal with any safety issues from investigational or marketed drugs:

1. Chair
   a. Medical Affairs/Safety Surveillance Group
2. Each of the following disciplines will review the data presented for the meetings and provide recommendations as to the course of action to be taken based on this information
   a. Scientific Affairs
   b. Clinical Operations
   c. Regulatory Affairs

From time to time, the ESRB core team may involve other departments in its meetings (i.e. marketing, labeling, pre-clinical, legal).

4.0 PROCEDURE

4.1 Meetings will be held on a quarterly basis with "as needed" meetings for additional needs that may arise throughout the year.

4.2 Medical Affairs will be responsible for scheduling meetings and coordinating activities. Medical Affairs SSG will also be responsible for compiling and disseminating data to the board members prior to each meeting.

4.0 PROCEDURE (Cont'd)

4.3 Meetings will be structured in the following general format:

- Review & approval of previous meeting minutes
- Status update on open action items
- Marketed Drug Review
- Periodic Safety Reports filed in previous quarter
- 15-day alert reports
- Trends versus other similar therapeutic categories.
  - Investigational Drug Review
    - Safety summary data from IND reports
    - Safety data from study final reports
    - Trends versus other similar therapeutic categories.
  - Wrap-up
    - Review of recommendations and timelines from current meeting.

4.4 The ESRB will examine the AE data looking for possible signals that may require further investigation, trial initiation to determine risk factors, or changes to the investigators brochure or package insert.

4.5 Action items will be assigned to the appropriate discipline with anticipated timelines for completion.

4.6 The ESRB meeting medical affairs representative will document, in the meeting minutes, recommendations based on the data presented for each product.

APPENDIX 6 - ENDO SAFETY REVIEW BOARD (ERSB) CONSTITUENTS

The following members constitute the Endo Safety Review Board (presented in alphabetical order).

BRADLEY S. GALER, MD
Group Vice President, Scientific Affairs

Bradley S. Galer, M.D., joined Endo in 2000 as Vice President, Scientific Affairs. In this role, he is responsible for the Departments of Clinical Research, Clinical Operations, Medical Affairs, and Clinical Education & Development. He also currently holds an academic faculty position as Adjunct Assistant Professor of Neurology at the University of Pennsylvania School of Medicine. In his career, Dr. Galer has served in academic medicine as a chronic pain neurologist, with positions in the Department of Pain Medicine and Palliative Care at Beth Israel Medical Center in New York, where he was Director of Clinical Studies, Co-Director of the Nerve Pain Disorders Clinic, and Associate Professor of Neurology at Albert Einstein College of Medicine. Previously, Dr. Galer was Assistant Professor of Neurology and Anesthesiology at the University of Washington School of Medicine and served on the faculty of the Multidisciplinary Pain Center for five years. He currently sits on of the Board of Directors of the Reflex Sympathetic Dystrophy Syndrome Association of America and is Director-at-Large for the Eastern Pain Association. Dr. Galer is a founding member and former chairman of the Pain Medicine Section of the American Academy of Neurology. He has published over 100 articles and book chapters regarding pain management and pain pharmacotherapy. He has co-authored the book "Clinical Guide to Neuropathic Pain" with Dr. Robert Dworkin and is sole author of the CD-ROM "Chronic Pain and Headache." Since its inception, he has been a Steering Committee member of the annual International Neuropathic Pain Conference. He is the founding Editor-in-Chief of the journal *Current Pain and Headache Reports*, and was the Associate Editor of *The Clinical Journal of Pain*, for which he now serves on the Editorial Board. In addition, Dr. Galer is an ad-hoc reviewer of manuscripts for many journals, including *Pain* and the *Clinical Journal of Pain*. He holds academic memberships in a many medical societies, including the International Association for the Study of Pain, The American Pain Society, The American Academy of Neurology, and The American Academy of Pain Medicine and the American Academy of Neurology. He was named in the 1998 "Best Doctors in America" for Pain Management/Neurology.

Dr. Galer received his MD from Albert Einstein College of Medicine in New York. He served his internship at Kaiser Foundation Hospital, his residency in Albert Einstein's Neurology Program, and Pain Fellowships at both Memorial Sloane-Kettering Cancer Center and University of California San Francisco. He obtained his BA in Biology-Psychology at Wesleyan University, Middletown, Connecticut.

ARNOLD GAMMAITONI, PHARMD
Director, Medical Affairs

Dr. Gammaitoni received both his bachelors and doctoral degrees in pharmacy from the University of the Sciences in Philadelphia (formerly Philadelphia College of Pharmacy and Science). Prior to joining Endo, his clinical practice experience included community pharmacy ownership and serving as co-founder and Vice President of Clinical Practice of a specialty company that provided pharmaceutical care services to terminally ill hospice patients. As Director of Medical Affairs for Endo, primary responsibilities include Phase IIIB/IV clinical trial design and medical information services.

ROLAND GERRITSEN VAN DER HOOP, MD, PHD
Group Vice President, R&D, Strategic Partnerships

Roland Gerritsen van der Hoop, MD, PhD, joined ENDO Pharmaceuticals in August 2003 as Group Vice President R&D, Strategic Partnerships, and has responsibility for Project Management and Regulatory Affairs. He received his MD and PhD in Utrecht, the Netherlands before joining Solvay Pharmaceuticals in 1989. In his 15 years in the pharmaceutical industry, Dr. Gerritsen van der Hoop has held numerous supervisory positions in Clinical R&D, Regulatory Affairs, Drug Safety and Surveillance, Statistics and Data Management, and overall R&D end-responsibility. Also, he functioned as the Chief Medical Officer and medical spokesperson for Solvay in the US, responsible for all safety matters for Solvay products in the US, both marketed products and those under development. He has published over 30 full-length articles.

RONALD J. GERSON, PHD, DAB T
Vice President, Development.

Dr. Gerson is currently Vice President of Development at Endo Pharmaceuticals. In this capacity he is responsible for all preclinical activities conducted to support drug development and registration including Toxicology, Drug Metabolism/Pharmacokinetics, Pharmacology, and Pharmaceutics Development. He also leads Endo's drug discovery program and the preclinical evaluation of early-stage in-licensing candidates.

Dr. Gerson received his BA in Chemistry from the State University College of New York at Cortland in 1974 and an MS in Pharmacology from the University of Maryland School of Pharmacy in Baltimore in 1977. He received his doctorate in Toxicology from the University of Rochester in 1983 where he researched mechanisms of cadmium and mercury toxicity in primary hepatocyte cultures under the direction of Dr. Zahir Shaikh. After receiving his doctorate in Toxicology, Dr. Gerson pursued post-doctoral training in Biochemical Toxicology in the laboratory of Dr. John Farber at Hahnemann University, exploring the role of oxidative stress in the genesis of xenobiotic-induced toxicity.

Dr. Gerson joined the Department of Safety Assessment at Merck Research Laboratories as a Toxicologist in 1984 serving as a Study Director. In this capacity he was responsible for the design and interpretation of rodent/non-rodent subchronic/chronic toxicity studies and rodent carcinogenicity studies. During his tenure at Merck, Dr. Gerson served as the Study Director for over 200 GLP/non-GLP Toxicology studies and assumed positions of increasing responsibility, ultimately being appointed Associate Director in 1991. In 1993, Dr. Gerson joined the Department of Toxicology at Sterling Winthrop Pharmaceuticals as Associate Research Director of Safety and Experimental Toxicology. Shortly after the purchase of Sterling Winthrop by Sanofi in 1994, Dr. Gerson joined DuPont Merck Pharmaceuticals as Director of Toxicology. Following the formation of the DuPont Pharmaceuticals Company in 1999, he was appointed Senior Director of Toxicology within the Department of Safety Assessment. At DuPont Pharmaceuticals Dr. Gerson was responsible for the scientific oversight of all preclinical toxicology and reproductive/developmental toxicity studies conducted to evaluate DuPont Pharmaceutical drug development candidates and for the design of safety assessment programs in support of drug development and registration.

During his tenure in the pharmaceutical industry, Dr. Gerson has been responsible for the preclinical safety evaluation of a broad range of pharmacologic agents including cardiovascular, antiviral, CNS, cancer, and imaging agents. He has written or directed the preparation of over eighteen IND/ERC packages and four NDA/MAA submissions, including worldwide drug registration submissions for Zocor and Sustiva.

Dr. Gerson is a member of the Society of Toxicology, the American Association of Pharmaceutical Scientists, and the Steering Committee for the ILSI HESI Alternatives to Carcinogenicity Testing Committee on International Harmonization. He is also Vice-President of the Regulatory and Safety Evaluation Specialty Section of the Society of Toxicology. Past professional activities have included membership on the ILSI Alternatives to Carcinogenicity Testing Working Group, the PhRMA Metabolites in Safety Testing Task Force and faculty member for the PERI course entitled a Primer in Non-Clinical Safety Assessment of New Pharmaceuticals lecturing on the design and conduct of carcinogenicity studies. Dr. Gerson has authored 17 peer-reviewed scientific papers and is Board Certified in General Toxicology by the

American Board of Toxicology.

KRISTIN LIVINGSTON, MBA
Project Director, Project Management

Kristin Livingston joined Endo Pharmaceuticals Inc. in December of 2001. In her role as Project Director she is responsible for managing the development of several strategic projects in the pain therapeutic area at Endo Pharmaceuticals. In this position, she managed the preparation of two NDAs that were submitted to FDA in December 2002. Prior to joining Endo, Kristin was in Project Management at DuPont Pharmaceuticals from 1990-2002 (in varying roles of increasing responsibility) and managed projects in the antiviral, CNS, cancer, and medical imaging therapeutic areas. In this role, she managed projects at all stages of development, including the submission of two NDAs. Although located at DuPont's Wilmington headquarters, she was directly responsible for the project management activities at DuPont's medical imaging business in North Billerica, Massachusetts. From 1985 to1990, Kristin served as a data manager in the cardiovascular, anti-infective, and anti-inflammatory therapeutic areas at DuPont Pharmaceuticals. Prior to 1985, Kristin served as a data manager in the cardiovascular and critical care therapeutic areas at American Critical Care in Waukegan, IL.

Kristin received her MBA in Health and Medical Services Administration from Widener University in 1992. She received her BS in Health Information Management at the University of Illinois at Chicago in 1983.

MARIE E. PINIZZOTTO, MD
Director , Global Safety and Pharmacovigilance

Marie Pinizzotto, MD joined Endo Pharmaceuticals Inc in June 2003. In her role as the Director of the Global Safety and Pharmacovigilance department, Dr. Pinizzotto is responsible for all activities related to the monitoring, reporting and pharmacovigilance of the safety profile of investigational and marketed products on an ongoing basis. This includes the management of potential risks associated with these products, ensuring compliance with FDA regulations on expedited and periodic reporting of adverse events, developing and adhering to corporate standard operating procedures, and actively contributing to drug development project teams, supporting the safety aspects of protocol development, study implementation, and conduct.

Prior to joining Endo, she was the Senior Director of Report Evaluation and Safety Surveillance for the Women's Health Division at Wyeth, where she was responsible for the development of the risk management plan for hormone replacement products. In her role at Wyeth, she also

chaired safety committees for the review of adverse events of clinical trials as well as marketed products.

Dr. Pinizzotto received her medical degree from Jefferson Medical College in Philadelphia. She served her residency at The Medical Center of Delaware, where she practiced obstetrics and gynecology for nine years; she currently remains on staff and participates in the training of medical students. She obtained her BS in Chemistry from the University of Pittsburgh, Pittsburgh, PA.

MARY ALICE RAUDENBUSH, MS
Vice President, Regulatory Affairs

Mary Alice Raudenbush, MS, joined Endo Pharmaceuticals Inc. in October 2000 as Director of Regulatory Affairs. Subsequently she assumed the position of Vice President of the Regulatory Affairs Department. This department has primary responsibility for providing regulatory oversight of all new drug development and registration and maintenance of all marketed products. The department is composed of the Regulatory Chemistry, Manufacturing and Controls group, the Regulatory Liaison group, the Product Labeling group, and the Document Archives and e-Publishing groups.

Ms. Raudenbush began her regulatory career in 1987 with Wyeth working in the Pain/Inflammation area. In 1995, she left Wyeth to join Aventis Pharmaceuticals (previously Rhone-Poulenc Rorer) in the Regulatory Respiratory/Allergy/Inflammation group.

In total she has over 16 years of pharmaceutical regulatory experience, which includes direct responsibility for submission and/or approval of over 20 INDs, 12 NDAs, multiple sNDAs, ANDAs, and various international submissions.

She received a Bachelor's of Science in Chemistry from Chestnut Hill College and a Masters of Science in Pharmaceutics from Temple University.

THOMAS G. SCHLAGHECK, PHD
Vice President, Clinical Operations

In 1983 Dr Schlagheck was awarded a PhD in Physiology with emphasis in gastrointestinal physiology and neonatal immunology from the University of Arizona. This was preceded in 1979 by a Master of Science in Nutrition & Biochemistry from the University of Kentucky and a Bachelor of Science in Biology from DePaul University in 1977.

Following a Postdoctoral Fellowship at Virginia Tech University during which the intestinal transcellular epithelial absorption of peptides was investigated, Dr Schlagheck spent 4 years Eastman Kodak as a Senior Research Bioscientist. During this time, basic research programs included the use of enteric and polymer coating technologies for the development of oral vaccines and oral administration formulations of peptides and proteins including insulin.

Dr Schlagheck spent 11 years at Procter & Gamble in the OTC Health Care Division and the Pharmaceuticals Division in positions of increasing responsibility. Responsibilities included the management of clinical research programs in several therapeutic areas including gastrointestinal, respiratory, analgesics, nutrition and cardiovascular. Following a 6-month international assignment in Europe, his final assignment was Section Head, Worldwide Clinical Operations, Cardiovascular Products.

In 1999, Dr Schlagheck accepted the position of Director, Clinical Operations at Algos Pharmaceuticals with responsibility for clinical research programs associated with the development of proprietary combination opiate analgesics and NMDA-receptor antagonists. In 2000, Algos merged with Endo Pharmaceuticals. Dr. Schlagheck's current responsibilities include management of clinical research studies for all developmental and marketed drugs. The Clinical Operations organization is comprised of Clinical Operations, Biometrics, Clinical Data Management, Scientific Communications, Clinical Supplies, and Business Management.

SAJAN VARUGHESE, PHARMD, MBA
Manager, Global Safety & Pharmacovigilance

Dr. Varughese serves as Manager, Global Safety & Pharmacovigilance at Endo Pharmaceuticals since May 2002. His primary role at Endo Pharmaceuticals is to manage pharmacovigilance staff and day-to-day pharmacovigilance activities, including review of all expedited reports and periodic reports prior to submission to FDA, and facilitating the Endo Safety Review Board. Prior to Endo, Dr. Varughese served as a Report Evaluation Safety Surveillance (RESS) Scientist at Wyeth-Ayerst Research. There he assisted the RESS physician in the review, analysis, and evaluation of suspected adverse reaction reports and prepared written responses to safety queries. He developed core data sheets and contributed to safety review team meetings. Prior to Wyeth, Dr. Varughese served as Drug Product Safety Associate at Aventis Pharmaceuticals. Dr. Varughese also has extensive clinical experience in the field of pharmacy from working in the hospital and retail pharmacy settings.

Dr. Varughese received his Bachelor's in Pharmacy and Doctorate in Pharmacy from University of Sciences in Philadelphia (formerly the Philadelphia College of Pharmacy and Sciences) in

September 1997 and May 1998, respectively. He received his MBA in Global Management from University of Phoenix in September 2003.